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Results of the Surgical Treatment for Mitral Stenosis

Analysis of One Hundred Consecutive Cases

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An analysis of the first 100 consecutive cases of mitral stenosis treated by commissurotomy is presented. Frank hemoptysis was noted in 25 individuals and systemic arterial emboli in 22 others; no recurrence of these complications was found one to three and one-half years after surgery. "Pure" mitral stenosis was present in 64, and an associated insufficiency in 27; in nine others there was an associated aortic insufficiency. A sinus rhythm changed to auricular fibrillation after surgery in 15; in nine the change was permanent. In one instance auricular fibrillation changed to sinus rhythm postoperatively. A rough correlation was found between the extremes of pulmonary artery systolic pressure and the clinical, roentgen and electrocardiographic findings Calcium was found in the mitral valves in 52 patients and did not, per se, predicate a poor functional result. No instance of rheumatic fever occurred postoperatively, even though 14 of 78 biopsied auricular appendages indicated rheumatic infection. Functional improvement occurred in 78 patients, and there were nine unimproved. There were 11 deaths due to surgery and two who died during this three-year follow-up from intercurrent infection.

FOR CENTURIES the therapeutic problems of heart disease both valvular and myocardial have been entirely in the province of the internist. With the recent development of intracardiac surgical procedures a major adjunct in the treatment of mitral stenosis has become available. Lest one be tempted to suspect that the surgical approach to the problem of mitral stenosis has been entirely the concept of the surgeon one has only to recall that an internist, Brunton,[1] in 1902, was the first to propose direct surgical reconstruction of the valve. Forty-six years elapsed before the proper and successful application of Brunton's principle was consummated in 1948.[2,3]

The purpose of this publication is to present complete data pertaining to our first 100 consecutive commissurotomies for mitral stenosis. Previous communications[4-7] have reviewed the painstaking and at times fruitless efforts of many investigators.[8-15] These reports have also detailed the pathologic and physiologic considerations of the valvular deformity, and the technical aspects of its surgical correction have been outlined before this association.[4-7] It is, therefore, sufficient to state here that mitral commissurotomy is a procedure in which the individual anatomic leaflets of the stenotic mitral valve are surgically separated (fig. 1). By incising the angles or commissures of the mitral slit a considerable degree of valve function can be re-established without the production of additional significant mitral insufficiency (fig. 2). It is to be noted that no valve tissue is removed, thus allowing the liberated although thickened and deformed valve leaflets

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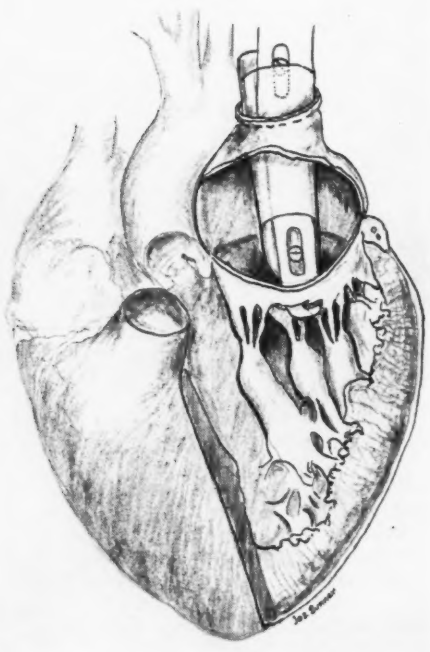

FIG. 1. Diagrammatic representation of the operative approach and technic of commissurotomy for mitral stenosis.

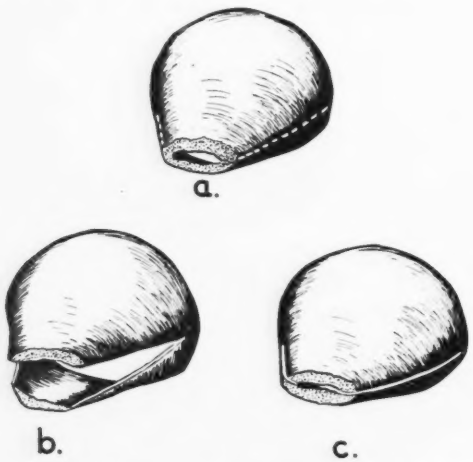

FIG. 2. Diagrammatic representation of the stenotic mitral cone as viewed from the left ventricle. (*a*) Line of incision in the anterolateral and posteromedial commissures. (*b*) The open valve cone during ventricular diastole. (*c*) Approximation of valve leaflets during ventricular systole minimizing regurgitation.

to open during ventricular diastole and approximate during ventricular systole.

ANALYSIS OF CASES

One hundred cases of mitral stenosis were treated by commissurotomy from March 22, 1948 to November 14, 1950. Of these, 64 were female and 36 were male. The youngest was age 17 and the oldest age 53. Most of these patients were far advanced in the course of their disease and represented the late or terminal stages of mitral stenosis. They have been grouped according to our previously published classification as follows:[16]

Stages of Mitral Stenosis

	Cases	Deaths
1. Asymptomatic	0	0
2. Statically incapacitating	6	0
3. Progressively incapacitating	63	7 (11%)
4. Terminally incapacitating	29	4 (14%)
5. Irreversible	2	2 (nonsurgical late deaths)

This classification has been prepared in an effort to combine a functional and therapeutic yardstick for evaluation of the patient for surgery. *Stage one* includes those with the auscultatory findings of mitral stenosis but who as yet have no symptoms. Cases in *stage two* have progressed to the point where symptoms under physical activity have developed, but the patient living within his own limitations remains on an even plateau. *Stage three*, the largest group, and one encompassing many variables includes those who despite the best medical therapy are losing ground. *Stage four*, terminally incapacitating, includes those patients in whom there is constant evidence of congestive failure even with limited physical activity. Most of these can be rendered relatively free of their accumulating tissue fluid only by the strictest of medical regime. A certain small percentage of those in this group will ultimately prove *after surgery* to have been in *stage five* and to have had irreversible changes. As yet, it has been impossible to routinely separate patients in these two stages by clini-

cal and physiologic methods, hence, we reserve stage five to classify those who, despite a technically adequate commissurotomy, receive no improvement.

Status Prior to Admission

Progressive dyspnea and fatigue were present in varying degree in each of the 100 cases. In addition to this evidence of cardiopulmonary disability, 32 had already progressed to the stage of right heart (congestive) failure as evidenced by one or more episodes of hepatomegaly, ascites and peripheral edema. Twenty-five had had one or more attacks of frank hemoptysis, in several instances to an almost exsanguinating degree. This does not include the many who had expectorated pinkish frothy material during bouts of pulmonary edema.

In 22, cerebral, visceral or peripheral emboli had occurred on one or more occasions. Of these, 19 had auricular fibrillation, three had sinus rhythm, and all had a history of one or more attacks of congestive failure. Interestingly, 10 of these 22 cases had gross thrombi in the left auricular appendage at operation. It is not unusual for the pathologist to report the presence of a small thrombus deep in the trabeculae of the excised appendage which was not noted during the commissurotomy. In one instance embolic episodes were appearing with such frequency that commissurotomy with ligation of the left auricular appendage was urgent.

Autopsy reports of the incidence of thrombi confined solely to the left auricular appendage vary. Graef and co-workers[17] found 47.4 per cent of 19 cases had thrombi limited to the left auricular appendage. Soderstrom[18] found left atrial mural thrombi in 50 cases of rheumatic heart disease. Mural thrombi were found in the left auricular appendage in 29 instances and on the main left atrial wall in 25 instances. No statement was made as to the number of cases in which thrombi in these two sites coexisted. Jordan and co-workers,[19] in a clinical and pathologic analysis of 51 cases of mitral stenosis, found 20 (47.6 per cent) of 42 cases with the thrombi limited to the left auricular appendage. In 22 (54.6 per cent) of these 42 cases, the thrombi in the left side of the heart were situated on the main atrial wall, in the auricular appendage and on the main atrial wall together, or in the left ventricle.

There have been no recurrent embolic episodes in any of these 22 cases (longest three years). It has been previously emphasized that ligation of the base of the left auricular appendage was responsible for this result. However, relief of stasis in the left atrium may be a major factor in preventing these recurrences.

Status Upon Admission (table 1)

In the initial phase of this surgical program every attempt was made to select cases of relatively "pure" mitral stenosis to insure a proper base line for evaluation of the surgically treated stenotic valve alone. It has since become apparent that the auscultatory findings of a minimal systolic mitral and/or aortic systolic or diastolic murmurs in addition to the classic mitral diastolic murmur may be of little consequence provided mitral *stenosis* is the *predominant factor* in the production of the patient's disabling symptoms. For this reason a number of cases were originally deferred for surgery until the eventual picture became clear. Sixty-four cases were classified as "pure" mitral stenosis in that there were no murmurs other than a diastolic rumble *at the apex*. This diagnosis was corroborated at the time of surgery when no regurgitant jet could be felt by the exploring finger. In 27 cases, there was an associated minimal (grade II systolic murmur) mitral insufficiency, and in two others there was aortic insufficiency of minimal degree. In seven individuals a mitral

TABLE 1.—*Admission Findings*

1. "Pure" mitral stenosis	64
2. Mitral stenosis with insufficiency	27
3. Mitral stenosis with insufficiency and aortic insufficiency	2
4. Mitral stenosis and aortic insufficiency	7
5. Left ventricular enlargement (x-ray). (Minimal to moderate)	12
6. Arrhythmias	57
7. Congestive Heart Failure	18
8. Electrocardiogram: RAD	77
NAD	21
LAD	2

diastolic rumble and an aortic diastolic murmur were the only murmurs heard.

In selection of cases for surgery, it is obvious that the careful auscultatory examination by an experienced cardiologist is paramount. The recognition of a typical uncomplicated mitral stenosis by stethoscopic methods usually presents no problem. The difficulty does not lie with this type of individual but rather with the patient who presents evidence of coexisting mitral stenosis and insufficiency, or multivalvular disease. Here, one must decide whether the mitral stenosis is the predominant lesion. Expert fluoroscopic and radiologic evaluation, with emphasis on individual chamber enlargement can be of inestimable value in this respect.

Eighty-eight of the cases presented a normal left ventricle, and in 12 there was minimal to moderate enlargement. In these 12, mitral insufficiency or associated aortic valvular disease was dynamically expressing its presence by enlargement of the left ventricle, a finding which we have come to regard as evidence tending to contraindicate surgery. Slight enlargement of the left ventricle due to mitral insufficiency is not an absolute contraindication but suggests the possibility of a more equivocal surgical result. If left ventricular enlargement is due to an aortic valvular lesion, commissurotomy would seem to be inadvisable at this time. The recognition of minor degrees of left ventricular enlargement in the presence of a markedly enlarged right ventricle may well be perplexing. Enlargement of all chambers of the heart is an absolute contraindication.

Auricular fibrillation, per se, is not a contraindication to surgery unless the ventricular rate is entirely uncontrollable. Fifty-seven patients had auricular fibrillation, and the results in these compared favorably with the results in those who had sinus rhythm.

Eighteen patients presented themselves in various stages of congestive heart failure although others were known to have been in this state prior to admission. Failure was controlled before surgery in all but four in whom failure had existed for many years. With the exception of minimal evidences these too eventually responded. The period of medical preparation of patients in this status was more prolonged, and in several instances six weeks or more were required. Some of the more dramatic results were achieved in this group after a prolonged period of convalescence.

The importance of hypertension of the pulmonary circulation in the natural history of mitral stenosis has been appreciated for many years. Such classic symptoms as dyspnea, orthopnea and hemoptysis have been thought to be indications of increased pressure in the pulmonary vascular bed. The roentgenologist and pathologist have supported the clinician's opinion of the importance of pulmonary hypertension by describing hypertrophy of the right ventricle, marked enlargement of the left atrium and pulmonary artery, and sclerotic changes in the large and small pulmonary arteries.

In patients with mitral stenosis, right heart catheterizations have recorded high systolic pressures in the right ventricle.[20] Borden and co-workers[21] found a rough correlation between the degree of pulmonary artery hypertension and the clinical manifestations. Comparable findings and correlations were observed in 72 of our 100 patients, in whom catheterization of the right heart was done. The upper limits of the pulmonary artery pressure found in this laboratory in normal subjects is 30/10 mm. Hg. As might be expected the higher the pressure in the pulmonary artery the closer the correlation with the clinical and roentgen findings. Usually a systolic pulmonary artery pressure of 50 mm. Hg or greater was associated with a history of prolonged functional disability, episodes of acute pulmonary congestion, hemoptysis or congestive failure. Such pressures, also, were commonly associated with fluoroscopic and x-ray evidence of marked left atrial and right ventricular enlargement and dilated pulmonary arteries. Electrocardiograms in about 75 per cent of this group showed right axis deviation (plus 90 degrees or more), thus reflecting somewhat the degree of pulmonary hypertension.

Chart 1 presents the results of commissurotomy upon the pulmonary arterial pressure. Seventy-two patients were catheterized before

and a number at 1, 6, 12 and 23 months after surgery.

Nineteen had pressures varying from 100 systolic, 35 diastolic to 148 systolic, 61 diastolic, the mean pressure ranging from 57 to 90; the average figures were 117 systolic and 50 diastolic, with a mean of 77. In all instances there was a drop in pressure after surgery, the average drop being 43 mm. Hg systolic, and 21 diastolic and 33 mean.

and sustained rise in pressure roughly paralleled her stormy postoperative course, which was beset with frequent episodes of pulmonary congestion, congestive heart failure and a progressive downhill course.

Pulmonary artery pressures ranging between 60 to 78 systolic and 23 to 38 diastolic were recorded in 10. After commissurotomy there was a drop in the systolic pressure from 69 to 51 mm. Hg systolic and a drop from 30 to 20

CHART 1.—*The Results of Commissurotomy on Pulmonary Arterial Pressure 1 to 23 Months Postoperative*

Pressure mm. Hg	Cases	Systolic (mm. Hg)			Diastolic (mm. Hg)			Mean (mm. Hg)		
		Preop.	Postop.	Fall—F Rise—R	Preop.	Postop.	Fall—F Rise—R	Preop.	Postop.	Fall—F Rise—R
100–150	19	117 (110–148)	74 (36–101)	43—F (8–112)	50 (35–61)	29 (15–37)	21—F (0–46)	77 (57–90)	44 (22–58)	33—F (7–68)
80–100	9	88 (81–96)	56 (48–76)	32—F (9–48)	32 (20–40)	20 (3–29)	12—F (0–21)	50 (45–56)	32 (18–43)	28—F (2–27)
	1	81	121	40—R	36	55	19—R	51	77	26—R
60–80	8	69 (60–78)	51 (35–75)	18—F (3–31)	30 (23–38)	20 (15–28)	10—F (4–23)	44 (37–51)	30 (21–41)	14—F (3–24)
	2	64 (60–68)	78 (66–89)	14—R (6–21)	29 (28–29)	33 (27–39)	4—R (1–10)	40 (38–42)	48 (40–55)	8—R (2–13)
40–60	17	51 (40–55)	40 (28–50)	11—F (2–17)	22 (13–27)	18 (10–23)	4—F (3–6)	31 (22–36)	25 (16–32)	6—F (3–11)
	5	49 (40–54)	64 (58–70)	15—R (3–30)	23 (17–36)	32 (24–41)	9—R (3–18)	31 (26–41)	43 (37–51)	12—R (3–18)
20–40	11	32 (22–38)	28 (18–42)	plus or minus	8 (6–12)	10 (8–14)	plus or minus	18	15	3—F
Total...	72									

There were 10 instances of systolic pressure between 80 to 100 mm. Hg. In nine of these the average drop in pressure after surgery was 32 systolic, 12 diastolic with a range of 9 to 48 systolic and 0 to 21 diastolic, the drop in the average mean pressure was 28. In one there was an increase in the pulmonary systolic pressure of 40 mm. Hg which represented an increase from 81 to 121 mm. Hg and was secondary to a severe mitral insufficiency produced at surgery. Interestingly, this marked diastolic in eight. Two of these 10 had an increase in the average systolic pressure from 64 to 78 mm. Hg. However, the clinical course, in both of these two patients, was considered to be markedly improved; thus, the increase in pressure did not indicate a poor clinical result.

Twenty-two had pressures varying between 40 to 55 systolic and 13 to 36 diastolic. Seventeen of these had a drop in the average systolic pulmonary artery pressure of 11 points, and five had an increase in pressure of 15. The

latter five showed improvement clinically. Again, as noted above, the clinical status was not closely correlated with the pulmonary pressure.

In 11 individuals, pressures varying between 22 systolic, 6 diastolic and 38 systolic, 12 diastolic were recorded. There was no significant rise or fall in the pressures postoperatively. In this group we found minimal symptoms and no instance of hemoptysis.

There is a wide range of pressures, probably between 40 to 80 mm. Hg systolic which cannot be closely correlated with the clinical state. These statements are speculative, but a review of our results indicates that only the extreme ranges can be correlated with the functional state. In other words, people with pressures of 80 mm. Hg or above usually have definite evidence of functional incapacity. In this range one expects orthopnea, nocturnal dyspnea, hemoptysis and congestive heart failure. Whereas, those individuals with pressures of 40 mm. Hg systolic or less usually have minimal symptoms, although not infrequently the complications associated with mitral stenosis such as auricular fibrillation and embolic phenomena are found.

It must be borne in mind that most of the above postoperative pressure readings were obtained within a month or two after surgery at a time when maximum changes could hardly be expected. Five patients have now returned for recatheterization after the lapse of over a year. In one patient a pressure of 57 systolic, 24 diastolic fell to 40 systolic, 19 diastolic, within one year. A dramatic change was noted within 15 months in one instance by a change of pressure from 148 systolic, 56 diastolic, to 36 systolic, 15 diastolic, a drop of 112 mm. Hg systolic. Initial pressures in one patient of 90 systolic, 40 diastolic dropped to 60 systolic, 35 diastolic within 21 months. Pulmonary arterial pressures of 48 systolic, 16 diastolic were found to be 27 systolic, 10 diastolic, 23 months later. In another individual right ventricular pressures only were obtained. The initial systolic pressure was 68 mm. Hg; six months later it had risen to 89 mm. Hg. The last pressures obtained were 16 months after the initial ones, when a systolic of 53 mm. Hg was recorded.

Correlation of Clinical Findings with Pulmonary Pressures

(a) *Hemoptysis.* Twenty-five patients had frank hemoptysis; 12 of these patients had pressures ranging between 100 to 148 mm. Hg systolic; six between 80 to 100 mm. Hg; four between 60 to 80 mm. Hg.; and three occurred between 40 to 60 mm. Hg.

(b) *Congestive Heart Failure.* There were 18 instances of congestive heart failure. Nine had pressures greater than 100 mm. Hg systolic; four varied from 80 to 100 mm. Hg; three fell between 60 to 80 mm. Hg; one between 40 to 60 mm. Hg; and one had a pressure of 34 mm. Hg systolic. This latter case was one of far advanced failure in a 47 year old white female with aneurysmal dilatation of the left atrium and a tight mitral stenosis, who had been at complete bed rest for one year. We have noted an occasional relatively normal pulmonary artery pressure in these individuals with congestive failure who have been at bed rest for a long period even though the mitral orifice is found to be the size of the head of a paper match at operation.

(c) *Graham Steell Murmur.* There were six individuals in whom a soft diastolic murmur was localized in the second left intercostal space. There was no change in the quality or intensity with change in position or respiration, and no other murmur could be heard at the base. It was thought that we were probably dealing with a Graham Steell murmur. At operation the pulmonary arteries were enormously dilated (three times the normal), and tense. These findings and the subsequent disappearance of the murmur after surgery seemed to confirm the original diagnosis.

(d) *Arrhythmias.* There was no correlation between the presence of auricular fibrillation or supraventricular tachycardia and pulmonary artery pressures.

(e) *Roentgenologic and Electrocardiographic Correlations.* A mild hypertension usually was associated with slight enlargement of the left atrium and straightening of the left border of

the heart. However, no definitive correlation between the size of the left atrium or right ventricle and the degree of pulmonary hypertension could be made.

Right axis deviation (plus 90 degrees or more) was observed in 77 patients, most of whom had pressures of 50 mm. Hg systolic or greater. However, no exact correlation between the pulmonary arterial pressure and the degree of the axis shift could be made.

The prediction of the x-ray and electrocardiographic findings can usually be made more precisely from the physical examination and a history indicative of sustained pulmonary hypertension, than from the pulmonary artery pressure per se.

TABLE 2.—*Operative Findings*

1. Size of valve orifice (estimated)	
(a) 0.5 cm. (no regurgitant jet)	72
(b) 0.5 cm. up to 1.5 cm. (regurgitant jet in 14)	28
(c) Orifice after commissurotomy	
2.5-3.5 cm.	86
1.5-2.5 cm.	5
1.5 cm.	9
2. Calcification of valve	52
3. Thrombi	15

The electrocardiogram frequently aids in determining the candidacy of these patients, especially when there is more than one valve defect. Evidence of right ventricular enlargement suggests that the predominant lesion is one of mitral stenosis. It is to be noted that a right axis deviation (plus 90 degrees or more) was present in 77 cases, a normal axis in 21, but more particularly that in only two instances was there evidence of a left axis shift. These latter two occurred in patients with multivalvular lesions and at operation both had major mitral regurgitation. Finding a left axis shift predicates that other factors are at play and a careful re-evaluation must follow.

Operative Findings (*table 2*)

Seldom in the past has there been the opportunity to examine at first hand the nature of living valvular pathology in situ. It has been a source of wonder to the authors to find the average stenotic valve in relatively good condition when contrasted to the incapacitation of the patient.

1. The size of the valve orifice as estimated by the tip of the exploring index finger in 72 of the cases was approximately 0.5 cm. in diameter or, in more readily appreciated terms, the size of the head of a paper match stick (fig. 3). The cusp margins were thickened, and fibrotic with fixation of the periorificial ring. Nevertheless, just enough pliability remained so that no regurgitant jet of blood could be detected with ventricular systole. In the remaining 28, the orifice was somewhat larger, being 0.5 cm. to 1.5 cm. (one to three match heads) and in 14 of these a distinct regurgitant jet could be appreciated.

FIG. 3. Autopsy specimen of nonsurgical patient illustrating the size of the mitral orifice reduced to 0.5 cm. (match head) in longest diameter as observed from the ventricular aspect.

In contrast to the firmer cusp margins the thickened valve leaflets proper are considerably more flexible. Thus, the "mitral megaphone" (fig. 2*a*) with its ventricular mouthpiece rides back and forth as a complete cone in response to changes in pressure on its two sides, always maintaining its construction and unable to open or close at its orifice.

2. Calcification was present in some measure in 52 of the valves. The frequent site for such infiltration was on the anterior valve leaflet over its medial aspect—that portion nearest

the outflow tract of the left ventricle. Many of the valves were lightly flecked with tiny calcific beads along the cusp margins. In others the calcium extended back into the leaflets for varying distances at one or more points of the circumference. Even in these situations considerable mobility could be frequently restored by commissurotomy. In 10 cases calcium was present in larger quantity practically encircling the mitral orifice and appreciably limiting the reconstructive effect obtainable by incising the commissures. Three of these were essentially inoperable. Fortunately the anterolateral commissure is less frequently involved by calcium and separation at this point will improve the patient as a rule, regardless of the status of the remaining valve cone. It is to be emphasized, therefore, that the presence of calcium, per se, need not necessarily mitigate against a good functional result. Occasionally, without detectable calcium, the circumferential contraction of the atrioventricular ring together with extreme thickening of the valve cone and foreshortening of the chordae tendineae result in such fixation that commissurotomy is unavailing.

TABLE 3.—*Postoperative Status*

1. Chest Pain	100
(a) Intercostal	100
(b) Pleuropericardial	30
2. Pericardial effusion	7
3. Arrhythmias	15
4. Postoperative hemiplegia	3
5. Reactivation of rheumatic infection	0
6. Auscultatory changes	100

3. Gross evidence of thrombosis was encountered in the left auricular appendage of 15 patients. Arterial embolization was associated in 10 of the 15 patients and auricular fibrillation in 14. Five patients with thrombosis and auricular fibrillation had no embolic episodes. Interestingly, there was pathologic evidence of rheumatic activity in the excised appendages of four (27 per cent) of the 15 cases. The role such activity plays in thrombus formation in mitral stenosis may be significant.

Immediate Postoperative Status (table 3)

1. *Chest Pain.* (a) The usual thoracotomy pain, intercostal in type, is to be expected and was experienced by all patients. Its duration is usually for 10 days and is relieved by sedatives. (b) Pleuropericardial pain may be a striking sequel to this surgery and is much more severe and persistent than that experienced by the average thoracic surgical patient. It occurs in about 30 per cent of cases and most frequently during the second postoperative week. However, it may occur sporadically and recurrently at any time during the ensuing six months. The pain is typical of that seen in acute pericarditis and similarly is aggravated by swallowing and change of position. The usual location of the pain is the lower substernal area either localized or radiating to the neck or back, or it may begin posteriorly. In approximately 5 per cent of these a small pleural effusion develops.

The importance of this pain lies in the fact of its persistence, severity, unpredictability and its lack of response to salicylates, antibiotics, and ordinary doses of narcotics. In one extreme instance this distress persisted daily for three months and precipitated right heart failure. Although this morbidity was unusually long the patient has now been symptom free for two and one-half years and has returned to normal activity. An attempt has been made to anticipate the probable onset of this complication by investigating the patient's rheumatic state prior to surgery. Unfortunately we are unable to predict with any certainty such a complication, either from the history, physical examination or laboratory studies.

2. *Pericardial Effusion.* There were seven instances in which pericardial aspiration seemed desirable. This type of effusion is not associated with the usual signs and symptoms of cardiac tamponade. The exhibition of undue anxiety associated with a feeling of strangling and oppression should arouse suspicion. The apical rate may be normal or slightly elevated; slight orthopnea and hyperpnea may develop with profuse perspiration and as a rule the systolic blood pressure is lowered. The jugular veins infrequently are distended. Although the physical findings are not typical for effusion, pericardiocentesis will yield 3 to 6 ounces of serosanguineous fluid often containing clotted blood. Even as the

fluid is withdrawn the patient experiences subjective relief. Repeated aspiration has not been necessary.

3. *Arrhythmias.* Auricular fibrillation developed postoperatively within the first four days in 15 individuals who had been in sinus rhythm prior to surgery. Six were transient and returned to a sinus mechanism without the use of quinidine, and nine became permanent.

One instance of auricular fibrillation reverted to sinus rhythm after surgery and remained so for seven months, when the patient died of streptococcal pneumonia with septicemia.

4. *Postoperative Hemiplegia.* Three patients awoke from anesthesia with an hemiplegia. In two of these no evidence of gross thrombosis had been observed in the left auricular appendage so that the origin of the embolus is unknown. Thrombotic material was present in the appendage of the third and presumably this was the embolic source. Immediate therapeutic stellate ganglion novacain blocks were done and repeated as indicated. Each made an uneventful recovery except for a minor motor weakness of one extremity.

5. *Reactivation of Rheumatic Infection.* There was no instance of an exacerbation of acute rheumatic fever following surgery. This was unexpected in view of the histologic evidence of the rheumatic state in 14 of 88 amputated appendages as disclosed by one of us (J. E. G.) (fig. 4). A higher incidence of rheumatic stigmata might be expected if the myocardium proper also had been examined. The previously described postoperative pleuropericardial episodes have been considered by the authors to be possible manifestations of smoldering rheumatic activity but direct evidence is lacking. Further observation will be necessary before the role of rheumatic infection as influenced by surgery can be evaluated.

6. *Auscultatory changes.* A loud pericardial friction rub was almost invariably heard immediately after surgery, disappearing slowly within 10 days.

The mitral diastolic rumble was usually greatly diminished in intensity and during the first 7 to 10 days may be inaudible. Less frequently, one may note an increase in the intensity of the diastolic rumble, probably due to increase in the rate of blood flow after commissurotomy.

In almost all of the cases a mitral systolic murmur was produced. Its usual intensity may be graded as I to II and this murmur usually persists. It is felt that as a rule this murmur does not represent a significant degree of insufficiency.

The sharp and accentuated mitral first sound usually remains unchanged in quality even though the diastolic rumble may disappear.

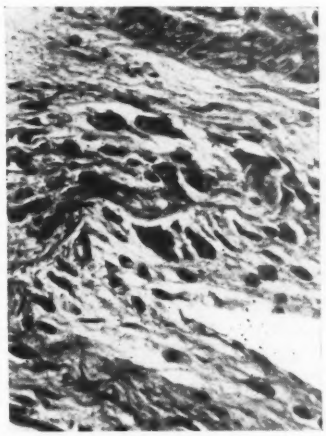

FIG. 4. Microscopic section of surgically removed left auricular appendage. Represents a definite endocardial Aschoff body. There is a wide curved band of centrally placed collagen showing "fibrinoid" necrosis surrounded by several typical Aschoff cells, several Anitschcow myocytes and other cells.

This sound appears to be the least affected by mitral valve surgery. The pulmonic second sound frequently remains accentuated, even though the pressure in the pulmonary artery has been reduced.

Thus, to summarize, the murmurs may change materially but the individual heart sounds may not.

Present Functional Status (table 4)

There is no more difficult a task in the compilation of clinical data than to reach agreement on suitable and self explanatory criteria for the evaluation of surgical results. This is especially true when the pathologic and physiologic patterns of a disease entity, such as mitral

stenosis, are so varied. The common ground for comparison would seem to be the functional status of the patient observed one or more years after surgery.

TABLE 4.—*Present Functional Status (one to three and one-half year follow-up)*

1. Excellent	32	
2. Improved	46	
3. Unimproved	9	(2 have recently died)
4. Mortality	11	
(a) Deaths not due to surgery	2	

Table 4 summarizes the results as obtained in this series. Thirty-two patients are classified as being *excellent* in that they have been restored to a normal productive life, enjoying all normal activities, without obvious limitation, while no longer requiring cardiac medication. Forty-six patients are considered to be objectively (fig. 5) and subjectively *improved* as evidenced by their return to almost normal life and activity within their own particular limitations determined on a trial and error basis. Some of this group still require medication because of the demands of their more greatly enlarged sphere of activity. A few so incapacitated as to be placed in class IV, according to the criteria of the New York Heart Association,[22] have now become so amenable to therapy that reasonable activity requires digitalization only. The range of improvement in this group varies widely with the condition of the valve found at surgery and the degree to which valve function could be restored. Their progressive downhill course has been abruptly terminated or reversed, some to regain a high level of efficiency, and others to remain on an improved plateau.

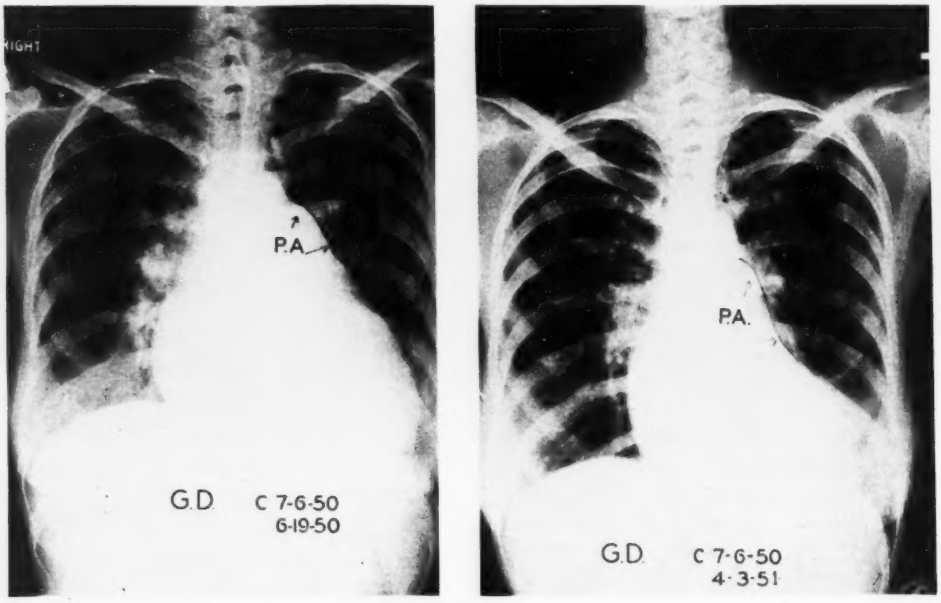

FIG. 5. Preoperative (left) and postoperative (right) chest films showing marked reduction in cardiac size nine months after surgery. Postoperative pleural reaction in left costophrenic angle partially obliterates lower left cardiac border.

Nine have been essentially *unimproved* and two factors were responsible for this. There were three with inoperable valves and six in whom significant mitral regurgitation was produced (fig. 6).

There were 11 deaths directly attributable to surgical technic. The first of these was the first case in this series. Postmortem examina-

tion revealed that the lateral commissure had not been opened more than a few millimeters so that death was occasioned by unrelieved mitral stenosis with the superimposed trauma of surgery. The second death occurred early in the series before the appendage was being ligated at its base. Thrombosis occurred in the appendageal lumen providing the source for subsequent fatal cerebral embolus occurring on the seventh postoperative day in a patient who had had a good technical commissurotomy.

which accurate and definitive incision in the commissures can more readily be controlled. A glance at figure 7 will reveal that our greatest mortality came at a time when the surgical technic was being developed. Certain of these deaths might have been obviated with our present experience.

There were four additional deaths for which surgery cannot be indicted. In two the selection of the cases was obviously poor since there was a marked degree of associated mitral

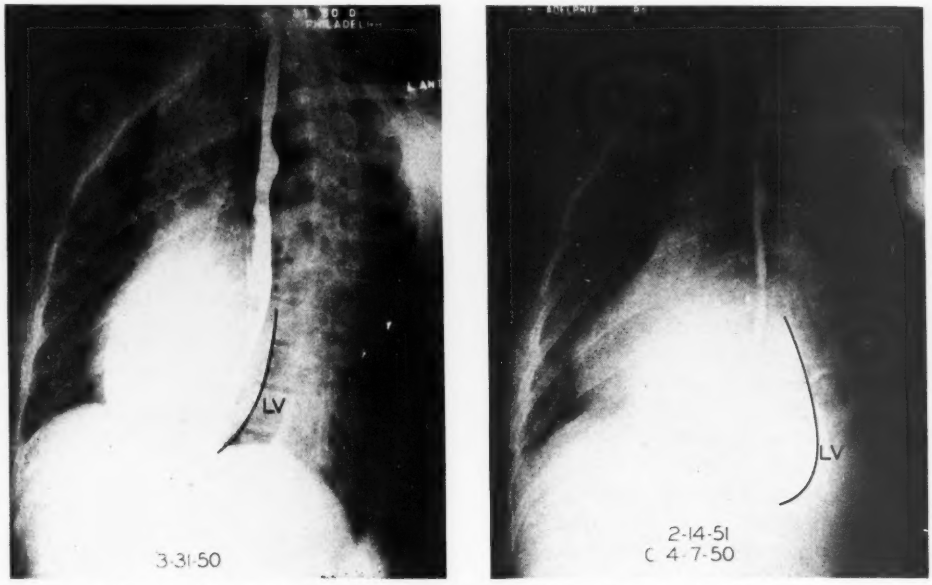

FIG. 6. Preoperative (left) and postoperative (right) oblique films showing the rapid increase in size of the left ventricle by the inadvertent surgical production of significant mitral insufficiency.

In two, hemorrhage occurred from the appendage—one 24 hours after surgery and the other during an ill-advised attempt to remove an adherent thrombus. One case remained in shock with peripheral vascular collapse for four days, cause unknown. In the remaining six cases surgically produced severe mitral insufficiency caused death, which occurred either in the operating room or within the first postoperative month. Most of these were occasioned by the use of finger dilatation, the line of valvular separation occurring either in the wrong place or extending too far. For this reason we have always preferred the use of a specially devised guillotine knife (fig. 1) with

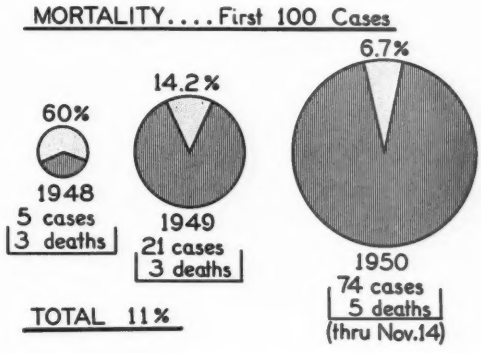

FIG. 7. Mortality—First 100 consecutive cases of commissurotomy for mitral stenosis.

insufficiency. Both died within seven months after surgery from unabated progression of their disease. A fulminating streptococcal pneumonia with septicemia was responsible for another death. The fourth died of an acute hemorrhagic pancreatitis.

Discussion and Conclusion

In the light of the foregoing presentation, the selection of patients for surgical intervention must necessarily be considered under seven major categories. These are outlined as follows:

1. History: (a) Early progressive cardiopulmonary dysfunction—ideal, (b) Marked dyspnea, hemoptysis, reversible congestive failure—acceptable.

2. Age—elastic range—physiologic rather than chronologic.

3. Valvular Defect: (a) "Pure" mitral stenosis—ideal, (b) Associated mitral insufficiency and/or aortic valve lesion in presence of normal left ventricle—acceptable.

4. X-ray: (a) Left atrium and right ventricle minimally enlarged—ideal, (b) Minimal left ventricular enlargement—acceptable.

5. Electrocardiogram: (a) Normal electrical axis or right ventricular strain—acceptable, (b) Left axis shift—*never* acceptable.

6. Functional Capacity: (a) Stage 2—statically incapacitating—ideal, (b) Stage 3—progressively incapacitating—acceptable, (c) Stages 4 and 5—debatable.

7. Complicating factors: (a) Arterial embolic episodes, and (b) Recurrent hemoptysis—both are acceptable, and may be urgent.

In conclusion, surgical reconstruction of the stenotic mitral valve is but a *major adjunct* in the continuing care of these rheumatic victims. Although such patients can and have been restored to a high level of efficiency and, as such, enjoy a more normal life, nevertheless they must always be considered as cardiac patients under the watchful care of their attending physicians just as the surgically treated tuberculous patient will require frequent observation, advice and management. With a greater understanding of the inherent nature of progressive mitral stenosis and the demonstration of a technically successful operation, both as to a lowering mortality rate and the satisfactory results obtained, the selection of patients at an early stage is of utmost importance.

Addendum

The personal series of the authors has been extended to 274 cases as of May 1952. The operative mortality has been 5.8 per cent. Marked and sustained improvement has been present in 76 per cent of the patients.

Acknowledgments

The authors wish to express their appreciation to Charles P. Bailey, M.D., Department of Thoracic Surgery, and George D. Geckeler, M.D., Lowell L. Lane, M.D., Franklin C. Massey, M.D., and William Likoff, M.D., Department of Cardiology, Hahnemann Medical College and Hospital for permission to include their cases along with our own to make this series chronologically consecutive.

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The Pathogenesis of Spontaneous Cardiac Rupture

By STANFORD WESSLER, M.D., PAUL M. ZOLL, M.D., AND MONROE J. SCHLESINGER, M.D.

Twenty patients with cardiac rupture were compared with suitable control groups. In each ruptured heart there was an acute coronary artery occlusion and a recent, transmural myocardial infarction which was unprotected at the site of rupture by scar or anastomotic circulation. Clinically, rupture usually occurred during the first two weeks of an acute infarction in a hypertensive patient with no previous history of old infarction or congestive failure; persisting hypertension or excessive effort usually preceded rupture. The role of an increased intraventricular pressure in the pathogenesis of cardiac rupture has therapeutic implications.

SUDDEN DEATH from rupture of the heart is so dramatic an event that it has interested both clinicians and pathologists since the time of Harvey.[1] Despite an extensive literature its exact causation is still not completely clear. New data concerning the pathogenesis of cardiac rupture are presented in this paper.

The term myocardial rupture usually denotes a complete, acquired defect through the muscular wall of one or more cardiac chambers. It, therefore, includes perforation of the interventricular or interauricular septum but does not refer to incomplete myocardial tear or rupture of the coronary arteries, coronary veins, cardiac valves, papillary muscles, chordae tendineae or aorta. In the absence of extracardiac causes rupture is said to be spontaneous.

METHODS AND MATERIALS

Between 1936 and 1950 a total of 1641 autopsies were performed at the Beth Israel Hospital, Boston, in which the hearts were adequately studied by a special technic of injection plus dissection of the coronary arteries.[2] Briefly this method consisted of (1) injecting a radiopaque lead-agar mass of different colors into the main coronary arteries, (2) unrolling the heart so that its entire arterial tree lay in one plane, (3) taking a roentgenogram of the unrolled heart, and (4) carefully dissecting the coronary arteries, using the film as a guide. With the aid of this special technic precise data concerning occlusions and narrowings in the coronary arteries and interarterial anastomotic pathways were obtained. The methods by which such occlusions, narrowings and interarterial anastomoses were determined have been described previously.[2]

In this series of 1641 injected hearts 19 instances of spontaneous myocardial rupture were found. In 14 of the ruptured hearts, multiple, carefully localized histologic sections of the myocardium were also available. Myocardial fibrosis and recent infarction were graded in these sections as absent, slight, moderate or marked. A twentieth ruptured heart that came from another hospital* was studied in the same way and is included in this report. The method of study and the technic used to record the data are illustrated in figures 1, 2*A*, 2*B*. In every one of these 20 ruptured hearts a recent myocardial infarct was found. Therefore, a similarly studied, control group of 104 hearts with fresh infarcts in which rupture did not occur was examined for comparative purposes. The clinical records of these 124 patients and of 104 additional patients who survived an episode of acute myocardial infarction were also carefully reviewed.

PATHOLOGIC OBSERVATIONS

1. *Incidence of Rupture.* The entire series of 1641 injected hearts contained 261 histologically proven acute infarcts including the 19 with rupture. Thus, the incidence of rup-

From the Medical Research Department of the Yamins Research Laboratories and the Pathology Department of the Beth Israel Hospital, Boston, Mass., and the Departments of Medicine and Pathology, Harvard University Medical School, Boston, Mass. This investigation was aided by grants from the American Heart Association, the Life Insurance Medical Research Fund, the U. S. Public Health Service and the Patrons of Research, Beth Israel Hospital, and was carried out during the tenure of one of the authors (S.W.) of a National Heart Institute traineeship.

* This heart was given to us for study by Dr. David Skinner, pathologist of the Newton-Wellesley Hospital. It was not included in the analysis of incidence of cardiac rupture at the Beth Israel Hospital.

ture was 1.2 per cent in the autopsy population and 7 per cent in the group with acute infarction.

2. *Location and Size of Rupture.* The ruptures were limited to the left ventricle and septum (fig. 1); six ruptures were through the anterior and nine through the posterior left ventricular wall; of five interventricular septal ruptures, one was anterior and four were posterior. The ruptures were extremely variable in size and shape on both epicardial and endocardial surfaces. Some were ragged, gaping holes, some linear slits and still others exhibited a V-shaped external opening. The tears on the epicardial surface were easily found and varied in length from 3 to 30 mm. The endocardial origin of the ruptures were often small and hidden behind trabeculae carneae; frequently they were demonstrated only after careful probing.

3. *Heart Weight.* The weights of the hearts in this series are presented in table 1.* No significant difference in weight distribution was found between the hearts with and without rupture.

4. *Heart Group.* The relative lengths of the right and left coronary arteries vary and form the basis for a classification of human hearts.[3] Rupture of the heart was not found to be related to this anatomic pattern of the coronary arteries (table 2).

5. *Coronary Artery Occlusion.* Old coronary artery occlusions antedating the acute infarct were present in only one third of the ruptured hearts but were found in three-fourths of the nonruptured controls. Furthermore, in hearts with old occlusions there were less than half as many old occlusions per heart among the ruptured hearts as among the control hearts (table 2). Thus, the incidence of old coronary artery occlusions was significantly† less among the ruptured hearts than in the control group.

Concomitant with this infrequency of old coronary artery occlusions was a high incidence of fresh occlusions in hearts with rupture. In every one of the 20 ruptured hearts there was a fresh occlusion in the coronary artery system; on the other hand fresh occlusions were present in only half of the nonruptured controls (table 2).

6. *Fibrosis.* As might be expected from the infrequency of old coronary artery occlusions, there was little myocardial fibrosis among the ruptured hearts. Areas of marked fibrosis were not found in any of the 15 ruptured hearts with multiple sections, and moderate myocardial fibrosis was found in only one instance. In contrast, two thirds of the control hearts showed either marked or moderate fibrosis (table 2). Furthermore, in all 15 ruptured hearts areas that were entirely free of fibrosis were found within the infarcted zone; similar unscarred areas were found within the infarcts in only one third of the nonruptured hearts.

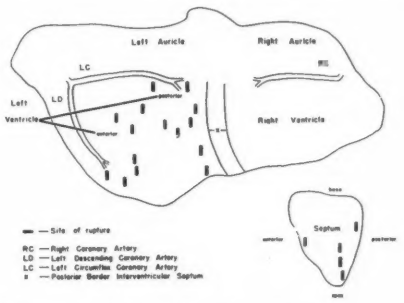

FIG. 1. Representative diagram of an unrolled heart in which the relation of the cardiac chambers and the coronary arteries is indicated. The sites of rupture in the 20 hearts in this study are also shown.

A myocardial aneurysm was not found among the group with rupture, but was present in 5 of the 104 control hearts.

7. *Size and Shape of Fresh Infarction.* The recent infarcts varied considerably in size in both the hearts with and without rupture; there was no significant difference between the two groups.

The transmural path of rupture, however, was not usually confined to a zone of infarction but traversed some noninfarcted myocardium. In every ruptured heart with multiple sections fresh infarction was found to ex-

* At the request of the editor, tables 1, 3, 4, 6, 8 and 9 are being eliminated but will be furnished upon request.

† Differences were considered to be statistically significant if they exceeded 2.5 times the standard error of the difference.

TABLE 2.—*Pathologic Findings in 124 Hearts with Acute Infarction (20 with Rupture; 104 without Rupture)*

	Rupture (20 Cases)	Control (104 Cases)
Heart Group I (Right coronary preponderance)	12	71
Heart Group II (Balanced)	4	22
Heart Group III (Left circumflex preponderance)	4	11
Number of hearts with old occlusions	7 (35%)	75 (72%)
Number of old occlusions	9	204
Number of hearts with fresh occlusions	20 (100%)	53 (50%)
*Amount of myocardial fibrosis absent	3	8
*Amount of myocardial fibrosis 1+	11	29
*Amount of myocardial fibrosis 2+	1	51
*Amount of myocardial fibrosis 3+	0	16
*Area of acute infarction without fibrosis	15 (100%)	38 (37%)
Myocardial aneurysm	0	5
*Size of acute infarct 1+	7	67
*Size of acute infarct 2+	4	15
*Size of acute infarct 3+	4	22
*Transmural infarct	15 (100%)	38 (37%)
Pericarditis	8	29
Mural thrombi	6	26
Intercoronary anastomoses	11 (55%)	91 (87%)
Collateral circulation poor within infarct	20 (100%)	40 (38%)

* Based on 15 of 20 ruptured hearts in which multiple microscopic sections were available.

tend across from endocardial to epicardial surface in one or more places, even though most of the infarction was not usually transmural. In only one third of the hearts without rupture were the fresh infarcts transmural (table 2).

The age of infarction was estimated in each available microscopic section according to the criteria of Mallory, White and Salcedo-Salgar.[4] Although many sections were taken, the age of every zone of infarction could be determined adequately in only 8 of the 15 ruptured hearts with multiple sections. In all eight the acute infarction was found to vary in age in different areas. This is also true of most fresh myocardial infarcts in which multiple sections are studied.[5] In these eight hearts the path of the rupture always traversed the area of most recent infarction that was also entirely free of fibrosis. In six of these eight carefully studied ruptured hearts the tear occurred at the junction of the most recently infarcted muscle and histologically normal myocardium.

8. *Pericarditis and Mural Thrombi.* Together with the transmural extension of the infarcts, the ruptured hearts more often presented a fibrinous pericarditis or a mural thrombus than did the hearts with nonruptured infarcts (table 2). Neither process apparently afforded protection against rupture.

9. *Collateral Circulation.* Interarterial coronary anastomoses were significantly less frequent in the 20 ruptured hearts than in the 104 control hearts (table 2).

In all 20 ruptured hearts direct or anastomotic filling of the vessels with injection mass was incomplete or entirely absent within the area of fresh infarction, a condition found in only a third of the control group. In every instance the rupture occurred through such

an uninjected, presumably avascular zone. Mass injected into the coronary arteries did not leak from the torn edges of the ruptured myocardium in any instance. All the blood found in the pericardial sac after cardiac rupture must, therefore, have come from the chamber of the left ventricle or from torn coronary veins or capillaries rather than from coronary arteries.

10. *Mechanism of Death.* Major, commonly fatal pathologic conditions in addition to fresh infarction were present in 42 per cent of the 104 control patients (table 3). These included advanced valvular disease, multiple fresh occlusions in different coronary arteries, uremia, pneumonia, pulmonary infarction, intestinal obstruction, bowel gangrene, and massive hemorrhage into the brain, thorax or abdomen. These conditions may themselves have caused or hastened death before evolution of the infarct had been completed. Such an accessory lethal condition was found in only one (5 per cent) of the 20 cases with rupture (table 3).

11. *The Pathologic Substrate for Rupture.* These comparisons between acute myocardial infarcts that ruptured and those that did not rupture delineate the pathologic conditions common to all ruptured hearts. These are:

(1) a *fresh* coronary artery *occlusion*
(2) a *recent* myocardial *infarct*
(3) a myocardial infarct which is *transmural*
(4) a myocardial infarct which is *poorly supplied with collateral vessels.*
(5) a myocardial infarct in which *fibrosis* is *entirely absent in at least one area.*

These five factors form the common denominator or pathologic substrate of spontaneous cardiac rupture.*

In this study there were 115 consecutive hearts with acute myocardial infarction in which adequate multiple microscopic sections were available. Among these 115 hearts were 22 with the pathologic substrate for rupture; rupture occurred in 11. The remaining 11 may be regarded as hearts that might have ruptured. Eight of these 11 cases showed other accessory lethal factors which may have themselves caused or hastened death. Thus, only three cases (cases 63, 65 and 89) in the "potential" rupture group were pathologically

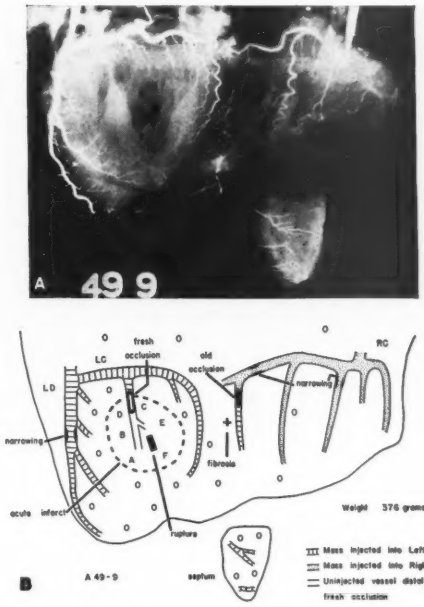

FIG. 2*A*, *B*. Roentgenogram and diagram of ruptured heart (case 16). "0" indicates absence of both fibrosis and necrosis. Slight fibrosis (1+ on scale of 0 to 5+) was found as indicated in only one of the 27 microscopic sections. Acute infarction, found in six sections (A–F) was graded in extent for each section (on scale of 0 to 5+). The age of the acute infarction varied from less than 1 to 10 days with section F showing the most recent infarction—all less than 24 hours' duration.

Section	Age Range of Infarct (Days)	Amount of Infarcted Muscle
A	10-	2+
B	10-2	4+
C	10-2	4+
D	10-1	3+
E	10-1	5+
F	<1	1+

indistinguishable from the group with rupture; death occurred in these three patients, four, five and eight days after the onset of acute infarction. On the basis of the pathologic data alone rupture might have been expected in

* The five ruptured hearts that lacked multiple, tagged, microscopic sections did fulfill all the criteria that could be determined in them.

these three hearts. An explanation for its absence must therefore be sought among the clinical phenomena occurring in patients with acute myocardial infarction.

Clinical Observations

The clinical data in all 124 patients, 20 with cardiac rupture and 104 controls with nonruptured acute infarcts, were reviewed in detail for distinctive features which might forewarn the clinician of impending rupture. In each instance the referring physician as well as the hospital record were consulted in order to check carefully the clinical details.

1. *Age.* The ages of the patients with and without rupture were listed in decades (table 4). No differences between the two groups are apparent.

2. *Sex.* Among the 20 patients with rupture, 11 were men and 9 women; among the 104 control patients without rupture there were three times as many men as women. The relatively high incidence of women among patients with cardiac rupture is not statistically significant in this small series.

3. *Hypertension.* For purposes of this study, arterial hypertension was considered to be present if either the systolic or diastolic pressure was 150 or 90 mm. of mercury, respectively, or higher. The readings were made under varied conditions in the outpatient clinics, by private physicians or in the hospital; they were subject to the many influences that inevitably prevail under these variable circumstances.[6] In the total series of 124 patients there were 13 in whom the usual blood pressure level could not be determined. These 13 equivocal cases, one of which occurred in the rupture group, were excluded from the present analysis. Hypertension was present in all of the remaining patients with rupture and in only two thirds of the control patients (table 5). This difference is significant. It was found, moreover, that the blood pressure remained elevated after onset of the terminal acute infarct in two thirds of the patients with rupture and in only one sixth of the control cases (table 5). This higher incidence of persistent hypertension during infarction in the group with rupture is also statistically significant.

4. *Congestive Heart Failure.* In considering the incidence of congestive failure prior to the terminal infarction, patients with congestive failure of less than one month's duration were

Table 5.—*Comparison of Clinical Findings in Patients with Acute Myocardial Infarction (1) Who Died with Cardiac Rupture, (2) Who Survived, (3) Who Died without Rupture*

		Prior to Terminal Infarction				During Terminal Infarction	
		Angina Pectoris	Congestive Heart Failure	Old Myocardial Infarction	Hypertension	Hypertension	Effort (during last 24 hours of life)
Acute Infarction with Rupture	+	10 (50%)	1 (5%)	0 (0%)	19 (100%)	12 (63%)	11 (55%)
	−	10	19	20	0	7	9
*(20 Cases)							
Acute Infarction with Survival	+	46 (44%)	8 (8%)	23 (22%)	56 (55%)	16 (16%)	
	−	58	94	81	46	86	rare†
*(104 Cases)							
Acute Infarction with Death but no Rupture	+	67 (68%)	34 (34%)	24 (25%)	63 (68%)	16 (17%)	22 (24%)
	−	31	65	72	29	76	70
*(104 Cases)							

* Totals do not equal 20 or 104 in all categories because of instances in which factors were not determined.

† Effort in this group of survivors refers to unusual effort at any time during the first three weeks of acute infarction.

omitted in order to eliminate those in whom the congestive failure may have been an associated symptom of the terminal infarction. The presence or absence of congestive heart failure was satisfactorily established on clinical and laboratory grounds in all but 5 of the 124 patients. These five patients, all in the control group, were omitted from this analysis. Congestive failure was present in only one of the 20 patients with rupture but was found in one third of the control patients (table 5). This difference is highly significant statistically.

5. *Angina Pectoris.* In evaluating the incidence of angina pectoris prior to the terminal infarction, patients with angina pectoris of short duration (less than one month before death) were omitted from the analysis in order to eliminate instances in which angina pectoris might have been entirely a prodromal manifestation of the terminal myocardial infarction. The presence or absence of anginal pain was clearly determined in all but six of the control group. Angina pectoris was present prior to the terminal infarction in half of the patients with rupture and in two thirds of the control patients (table 5). This difference between the two groups is not significant.

6. *Clinical Episode of Old Infarction.* The clinical diagnosis of myocardial infarction was accepted only after careful evaluation of the history, physical findings, clinical course and laboratory data which included leukocyte counts, erythrocyte sedimentation rates and electrocardiograms. A myocardial infarction was considered old or healed if it occurred more than two months before death. In eight of the control patients the presence or absence of a clinical episode of old myocardial infarction could not be determined with certainty. None of the 20 patients with rupture had a history of old infarction whereas it was present in one fourth of the control patients (table 5). This difference is probably significant.

7. *Effort during Terminal Infarction.* The amount of effort expended by a patient is difficult to quantitate clinically. The usual activities, physical and emotional, attendant upon enforced bed rest frequently produce excessive expenditures of energy. It is also true that occasional strenuous exertions by hospitalized patients are not always recorded or called to the attention of the professional staff. Furthermore, the duration of effort, its time of occurrence and associated circumstances may be of critical importance for its effect in producing myocardial rupture. In the face of these difficulties it was decided to limit analysis of this factor to "unusual" effort during the last 24 hours of life. Although use of the bedpan is associated with increased effort[7, 8] and although one of the patients with cardiac rupture actually expired on the bedpan, such activity was not included as unusual effort since it was so common among most patients hospitalized for acute infarction. Patients who were psychotic or sufficiently disturbed to require restraints or heavy sedation, patients who refused to stay in bed and those who were put through strenuous diagnostic procedures when the diagnosis of infarction had not been entertained, were considered to have experienced "unusual" effort.

In 12 of the 124 patients the presence or absence of unusual effort in the last 24 hours of life could not be determined: all 12 were in the control group. Sixty-one per cent of the patients with rupture and 24 per cent of the control patients experienced unusual effort (table 5). This is a significant difference. Of the 11 patients with rupture in whom unusual effort was noted within 24 hours of death, five were disturbed and psychotic, two refused to remain in bed, two were walking about, one had rapidly climbed three flights of stairs and one had undergone strenuous diagnostic tests during which marked elevations of the blood pressure had been recorded.

8. *Antemortem Diagnosis of Acute Myocardial Infarction.* In one patient from the rupture group and in seven control patients it was not clear whether the diagnosis of terminal acute infarction had been made during life. Acute myocardial infarction was diagnosed clinically in 90 per cent of the patients with rupture, but in only two thirds of the control cases.

In many of the 35 control cases with unrecognized myocardial infarction, the coronary heart disease was overshadowed by more prominent clinical conditions such as cerebral and gastrointestinal hemorrhage, pneumonia, uremia, dis-

secting aneurysm, surgical operations and pulmonary infarction. Furthermore, several of these clinically unnoticed infarcts were so small they were not recognized on gross pathologic examination but were found only after microscopic study of the myocardium.

9. *Clinical Diagnosis of Rupture.* Only 1 of the 15 ruptures through the left ventricular wall was diagnosed during life (case 14). In this instance the patient developed cardiac tamponade while being examined. Four of the five interventricular septal ruptures were correctly diagnosed or suspected during life on the basis of the sudden appearance of a loud systolic murmur after the onset of the infarction. The fifth patient (case 12) in whom the diagnosis of septal rupture was not suspected ante mortem had had a persistent loud

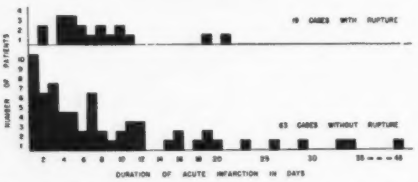

FIG. 3. Relation of time of death to onset of myocardial infarction.

rough apical systolic murmur for two years preceding the terminal illness. The duration of life from the recognition of the septal rupture to death varied from three hours (case 19) to nine days (case 6).

10. *Clinical Duration of Myocardial Infarction.* Among 19 patients with rupture in whom duration of the infarct could be determined, the interval from the clinical onset of infarction to death ranged from 2 to 21 days. Four-fifths of them expired between the fourth and eleventh days. In contrast, only one-third of the control patients died within this same time interval (fig. 3). This difference is statistically significant.

11. *Fever during Terminal Infarction.* The height and duration of fever was recorded sufficiently well in 87 of the 124 patients so that they could be classified into groups with absent or slight fever, moderate and high fever. No significant differences were found here between the patients with and without rupture.

12. *Leukocytosis during Terminal Infarction.* Leukocyte counts were recorded in 86 of the 124 patients. Although the determinations varied markedly in frequency from patient to patient, the 86 patients could be divided into three groups on the basis of the highest recorded counts: those with minimal or no elevation of the white count, those with moderate and those with marked leukocytosis. Here, also, no significant differences were noted between the patients with and without rupture.

13. *Electrocardiogram during Terminal Infarction.* Electrocardiographic tracings were recorded in 17 of the patients with rupture and in 81 of the control patients. The number of leads, and the number and timing of individual tracings varied considerably. Nevertheless, abnormal electrocardiograms were obtained in 97 of the 98 patients. Among the 17 patients with rupture the available electrocardiograms were consistent with a diagnosis of acute infarction in 14, abnormal but not diagnostic in two and entirely normal in one. The tracings were diagnostic of infarction in 50 of the control group and abnormal but not diagnostic in the rest. The incidence of diagnostic tracings was not significantly different in the two groups. The nondistinctive abnormalities in the two ruptured and the 31 control cases included variable atrioventricular block, bundle branch block, auricular fibrillation, auricular flutter, other arrhythmias and deviations of the S-T segments and T waves. In the one patient with a normal electrocardiogram (case 15) a normal 12 lead tracing was recorded seven days after the onset of the myocardial infarction and 48 hours before rupture. The roentgenogram and diagram of this patient's heart are shown in figures 2*A* and 2*B*.

14. *Drugs during Terminal Infarction.* The role of pharmacologic agents in the precipitation of myocardial rupture is difficult to evaluate. A wide variety of potent drugs was given in many different ways. Large doses of digitalis substances, quinidine, benzedrine, ephedrine, caffeine, Coramine, plasma, intravenous glucose and water, intravenous epinephrine, paraldehyde, mercurial diuretics, 50 per cent glucose in water, strychnine (case 27), aminophylline, prostigmine (case 41), papaverine, atropine,

heparin, magnesium sulfate, testosterone (case 101) and dicumarol (bishydroxycoumarin) were given to many of these patients with myocardial infarction. The evidence is inadequate that any of these drugs caused rupture. Experimental studies in dogs[9] have indicated that dicumarol produces no adverse pathologic effects in freshly infarcted myocardium; clinical reports also have not shown this anticoagulant to be associated with an increased incidence of rupture.[10, 11] In one patient there was a striking temporal relation between the administration of a drug and cardiac rupture. This patient (case 2) was not suspected of having a myocardial infarction and was given 0.3 cc. of Pitressin (vasopressin) subcutaneously for the successful relief of abdominal distention; she died suddenly 65 minutes later from myocardial rupture and cardiac tamponade. Although the dose of Pitressin given to this patient was less than that recommended as a test for coronary insufficiency,[12] this drug is a profound coronary vasoconstrictor[13] and has produced myocardial damage in animals.[14] In man severe myocardial ischemia and sudden death have followed its administration.[15, 16, 17]

15. *The Clinical "Profile" of the Patient with Cardiac Rupture.* From these clinical data conclusions may be drawn concerning the type of patient in whom rupture is most likely to occur. Rupture usually develops between the fourth and eleventh day of an acute myocardial infarction in a hypertensive patient with no previous history of old myocardial infarction or congestive failure. The hypertension frequently persists during the period of infarction and "unusual" effort often occurs within 24 hours of rupture. Angina pectoris is equally common among patients with and without rupture. Rupture appears to occur as frequently in women as in men. Age, leukocytosis, fever and the use of cardiac drugs during the acute infarct bear no relation to the occurrence of rupture.

This clinical "profile" is limited in that it is based on a consideration only of patients who *died* during an episode of acute myocardial infarction. It does not appraise the likelihood of rupture among all patients with clinical acute myocardial infarction before they die. Accordingly, the clinical records of a third group of 104 consecutive patients who survived an episode of acute myocardial infarction were reviewed for analysis of the factors of hypertension, angina pectoris, old myocardial infarction, congestive failure and unusual effort (table 5).

Hypertension and angina pectoris preceded the acute infarction in half, old infarction in one fourth and congestive failure in one twelfth of those who survived. Elevated blood pressure persisting during the acute infarction was found in only 16 per cent of the patients. Unusual effort, as previously defined, was rare during the acute illness (table 5).

Hypertension and unusual effort were more frequent and old myocardial infarction was less common in the rupture group than among the other two groups. Since congestive failure, prior to the terminal infarction, was uncommon in the rupture group and in the survivors, patients who will die of rupture resemble closely patients who will survive such infarcts.

Discussion

The series of ruptured hearts presented here differs from others previously reported in that the coronary arteries and myocardium were studied with an adequate injection technic and with multiple labelled microscopic sections. In addition a large group of nonruptured control hearts was also examined by the same methods. Finally, the clinical data in the group of cases with rupture and in comparable groups without rupture were correlated with the pathologic observations.

This unique body of data has delineated a uniform pathologic substrate common to hearts with spontaneous myocardial rupture. This substrate consists of an acute coronary artery occlusion and a recent myocardial infarct which is transmural, poorly supplied by collateral circulation and in which fibrosis is entirely absent in at least one area. Regardless of the presence elsewhere in the heart of myocardial fibrosis or collateral circulation from previous coronary artery obstruction, these pathologic criteria select hearts which are totally unprotected by scar or anastomosis at the site of the acute infarction.

Occasionally rupture may be produced by direct injury to the heart[18]; rarely the cause may be indirect trauma,[19, 20] blast,[21] infection[22, 23, 24] or tumor.[25] In most reported instances, however, and as in all our cases, rupture took place through an area of recent myocardial infarction. Contrary to general belief cardiac rupture secondary to recent myocardial infarction is not a pathologic curiosity. It occurred in 9 per cent of 2609 patients who died with acute infarction in 29 general hospitals (table 6).

Rupture was found by others as well as ourselves to occur through large and small infarcts.[28, 32] When an infarct involves the full thickness of the wall, the muscle is said to break more easily as soon as granulation tissue appears.[40] On the other hand ruptures have been reported through spotty infarcts and through infarcts which did not reach the endocardium.[28] The path of such rupture may be determined in part by the arrangement of the muscle planes.[41] Special histologic characteristics have not been described for infarcts which rupture[26, 42]; some are necrotic and heavily infiltrated with polymorphonuclear leukocytes whereas others show relatively little softening.[28] Tedeschi[43] observed the perforation of an abscess within an area of fresh infarction. It has been suggested[44] that pericarditis occurring with an acute infarct may prevent or delay the onset of rupture.

Although myocardial rupture usually occurs within the first two weeks after the onset of infarction[28, 34, 36, 42, 44–47] it has occasionally been observed in the third week.[28, 36] The range in the present series was from 2 to 21 days. Mallory, White and Salcedo-Salgar[4] believe that after the third week rupture is rare and usually the result of some complicating factor such as another fresh infarction.

Rupture has been reported through old infarcts[42, 48, 49] and through myocardial aneurysms[42, 44, 49–53]. Such observations, however, are exceedingly uncommon. In several studies old infarcts and aneurysms were present in many hearts, but rupture occurred only through areas of fresh infarction.[28, 31, 34, 45, 54–56] Furthermore, among three series of cardiac aneurysms [57–59] no myocardial rupture was reported. Finally, Edmondson and Hoxie[28] noted that when scarring was present in the myocardium, the likelihood of rupture was only one-fourth as great as in unscarred hearts. These observations on the relation between rupture and acute and healed infarction are in accord with our own findings.

As in our series, rupture has been found usually to take place in a single tear through the left ventricle or less commonly through the interventricular septum. Rupture of the right ventricle does occur and has often been reported because of its relative infrequency.[48, 50, 60–68] Atrial rupture also occurs[50, 62, 63, 69–72] but is rare. Double ruptures perforating the interventricular septum and the wall of the left ventricle[73, 74] or both ventricles[51] have been observed; Morgagni[75] described a heart with three discrete ventricular ruptures and Muller[76] reported a septal rupture with nine complete perforations.

A fresh occlusion has usually been found when the coronary arteries of ruptured hearts have been examined[44, 48, 51, 72, 77–80]; it was found in all our hearts with rupture. Occasionally rupture has been reported to occur in hearts without a fresh coronary artery occlusion,[44, 48] or even with normal coronary arteries.[70, 81] Meticulous dissections of the uninjected coronary arterial tree, however, may uncover only about one half of the points of occlusion.[82] One cannot, therefore, be completely certain that the coronary arteries are normal unless they have been injected and carefully dissected.

A positive correlation between myocardial rupture and hypertension was suggested by de la Chapelle.[44] Later Edmondson and Hoxie[28] conclusively demonstrated that hypertension persisting after the onset of a myocardial infarct increased significantly the likelihood of rupture. Others[37, 47] have also recently emphasized the significance of hypertension.

The relation of exertion to acute myocardial infarction has been the subject of many recent communications.[83–91] Physical effort has been ascribed a role in the pathogenesis of myocardial rupture by many investigators,[11, 34, 37, 44, 47, 48, 50, 51, 72, 78] although denied by some.[28, 92] Rupture has been described during epileptic seizures.[93] There are many references to the

frequent occurrence of cardiac rupture in mentally disturbed patients.[39, 48, 75, 79, 94–109] In such patients an acute myocardial infarction is frequently unsuspected clinically and the patient is usually ambulatory. Similarly, there is a high incidence of rupture among coroners' cases[39, 51, 55, 110] in whom antemortem diagnosis and bed rest are also uncommon. Severe physical effort after the onset of acute myocardial infarction would seem to be a common factor responsible for the high incidence of rupture among these two groups of patients.

TABLE 7.—*Comparative Incidence of Cardiac Rupture in Autopsy Populations from General Hospitals, Mental Institutions, and Coroners' Series*

Year	Author	Hospital	City	Number of Autopsies	Cardiac Rupture	
					Number	Per cent
		General Hospitals				
1872–1925	Krumbhaar (48)	Philadelphia General Hospital	Philadelphia, Pa.	16,000	7	0.04
1922–25	de la Chapelle (44)	Bellevue Hospital	New York, N. Y.	1,525	4	0.26
1924–41	Edmondson (28)	Los Angeles County Hospital	Los Angeles, Calif.	25,000	72	0.29
1926–45	Wang (29)	Massachusetts General Hospital	Boston, Mass.	7,018	23	0.33
1931–48	Foord (31)	Huntington Memorial Hospital	Pasadena, Calif.	3,173	33	1.3
1935–40	Wartman (32)	Western Reserve Institute of Pathology	Cleveland, Ohio	2,000	7	0.35
1939–40	Diaz-Rivera (34)	Louisville General Hospital	Louisville, Ky.	1,250	5	0.40
1940–49	MacDonald (36)	St. Lukes Hospital	New York, N. Y.	1,636	8	0.49
—1928	Buckley (111)	New Haven Hospital	New Haven, Conn.	1,330	3	0.23
—1933	Benson (51)	Good Samaritan Hospital	Portland, Ore.	3,784	7	0.28
—1948	Cleland (39)	Royal Adelaide Hospital	Adelaide, Australia	6,000	12	0.20
		Total of General Hospitals		68,716	181	0.26
		Mental Hospitals				
1910–27	Stewart (104)	Warren State Hospital	Warren, Pa.	840	6	0.7
1920–30	Beresford (103)	Tooting Bec Hospital	England	2,374	31	1.3
1927–33	Peterson (105)	St. Peter State Hospital	St. Peter, Minn.	207	3	1.4
1935–39	Snyder (79)	Western State Hospital	Ft. Steilacoon, Wash.	490	9	1.8
—1941	Simburg (107)	Brandon Hospital	Brandon, Canada	470	2	0.4
—1948	Cleland (39)	Southern Australia Mental Hospitals	Australia	600	4	0.7
		Total of Mental Hospitals		4,981	55	1.1
		Coroners' Cases				
1937–43	Rabson (110)	—	New York, N. Y.	2,030	24	1.2
—1933	Benson (51)	—	Muitnomah County, Ore.	2,112	27	1.3
—1940	Martland (55)	—	Newark, N. J.	2,000	42	2.1
—1948	Cleland (39)	—	Australia	250	8	3.2
		Total of Coroners' Cases		6,392	101	1.6
		Special Series (Coroners' and Mental)				
—1944	Jetter (108)	—	Massachusetts	115	16	14.0

Cleland[39] compared the incidence of cardiac rupture in necropsies, all examined under the same auspices, from a general hospital, from mental institutions and from coroners' cases. He found a strikingly different incidence of cardiac rupture in the three groups: the lowest

was in the general hospital population, and the highest in the coroners' series. We have arranged 21 reported series comprising 337 cardiac ruptures in a total of 80,089 necropsies according to Cleland's classification. The percentage of rupture was 0.26 in the general hospitals, 1.1 in the mental institutions and 1.6 in the coroners' cases (table 7).

In comparison the number of ruptures in a special group reported by Jetter and White is of unusual interest.[108] They found an incidence of cardiac rupture of 14 per cent in a consecutive series of 115 necropsies performed on patients who died suddenly and unexpectedly in Massachusetts psychiatric hospitals. Although frequently referred to as evidence of the high incidence of rupture in mental hospitals, this series is, in fact, a doubly selected group in which the additive effect of coroners' cases and psychiatric patients is dramatically apparent.

Our own data are in agreement with the observations that hypertension and effort play a role in the production of cardiac rupture. In our series persistence of hypertension during the acute infarction or unusual effort during the last 24 hours of life were found in 15 of the 19 patients in whom these factors were determined. Among the remaining four, one had unusual effort 36 hours before death, and another three days before death. As mentioned earlier there were three hearts in the control group (cases 63, 65, 89) which were—aside from the absence of rupture—pathologically indistinguishable from the hearts with rupture. In not one of these instances was either sustained hypertension or unusual effort present during the acute infarction. On the other hand, several patients in the control series exhibited sustained hypertension or unusual effort without rupture; the hearts of these patients, however, did not show the appropriate pathologic substrate for rupture. The necessary conditions, both pathologic and clinical, must be present before rupture will occur.

More than a century ago Quain[112] noted that the sexes were equally represented in his series of ruptured hearts. Since then others have noted a relatively high incidence of rupture among women.[39, 65, 79, 101, 103, 113] In general, however, relatively little attention has been given to the sex ratio among patients with rupture. We have reviewed several series of ruptured hearts from general hospitals but have excluded medical examiners' cases in which there is a marked preponderance of males.[55, 114] This tabulation (table 8) confirms the equal sex incidence originally noted by Quain. Since coronary disease and myocardial infarction are more common in men[121] the fact that the incidence of rupture is equal among the two sexes indicates that rupture is more prone to occur in the female who has an acute myocardial infarction.

The reported differences between the sexes in the extent of coronary disease[122] and the presence of hypertension[123] assume significance because of the importance of these factors in the production of myocardial rupture. We have, therefore, reviewed 1018 unselected necropsies from the Beth Israel Hospital in which satisfactory injections of the coronary arteries were carried out. The sex, the number of hearts with old coronary artery occlusions, the number of occlusions per heart and the presence of hypertension, determined according to the criteria mentioned above, are presented in table 9. Coronary artery occlusions were significantly more common among men and hypertension significantly more common among women.

It has already been demonstrated that rupture tends to occur in the hypertensive patient with minimal previous coronary disease. Since women fit these requirements more often than men, the relatively high frequency of rupture in women may be caused, in part, by these factors. Males predominate in groups of patients with angina pectoris,[124] myocardial infarction[35, 119] or myocardial aneurysm.[58, 59] To our knowledge cardiac rupture is the only manifestation of coronary disease in which the usual male preponderance does not obtain.

It has long been noted that rupture tends to occur among older people. Gradually, it has become clear that the age of patients with rupture parallels that for myocardial infarction. In a review of men who died from coronary artery disease, Yater[56] found that rupture occurred more often in the older age groups. He

also found, however, that the incidence of hypertension increased with age in his series. Increasing hypertension, rather than coronary artery disease, may account for the higher incidence of ruptures among the older patients observed by him.

There is no fundamental difference in the pathogenesis of left ventricular and interventricular septal rupture. They have the same pathologic substrate and they appear in the same type of patient; their occurrence depends simply on the location of the infarct. Clinically, the important difference is in the mode of death; in the former exitus is rapid from cardiac tamponade; in septal rupture, death is less abrupt and usually results from congestive heart failure.

The antemortem diagnosis of ventricular wall rupture has rarely been made because of the rapidity of death. A fortuitous examination may reveal an unusual murmur[125, 126] or sudden cardiac tamponade (case 15) immediately prior to death. In contrast, the diagnosis of septal rupture can frequently be established or at least suspected ante mortem on the basis of a new loud systolic murmur and progressive congestive failure complicating the course of acute myocardial infarction.[76, 80, 127–135] Patients may survive for days or even months following a complete septal tear[76, 136]; survival for five years has been reported.[137] Intraventricular block has been observed in septal rupture,[76, 136–138] but the disturbance in conduction may have been due to the infarction per se rather than the septal perforation. Complete atrioventricular dissociation has not been reported and might not be expected to result from rupture, which usually involves the lower portion of the septum[80] (fig. 1).

Angina pectoris, previous healed myocardial infarction and congestive failure all have been observed prior to the terminal infarction in patients with rupture. The comparative frequency and significance of these symptoms, however, have not been clearly analyzed. Since the hearts of patients with rupture revealed little old coronary artery obstruction and slight myocardial fibrosis, one might expect to find minimal evidence of angina pectoris, old infarction or congestive failure among these patients. All 20 patients with rupture met these expectations in that none showed a healed infarction and only one had congestive failure. In this one instance (case 13) the congestive failure was probably due to hypertensive heart disease since pathologic examination showed cardiac hypertrophy, very little myocardial fibrosis and no valvular disease. Angina pectoris, however, preceded the terminal infarction in half of the group. This incidence of angina was the same as that in the control group, although in the latter there was a significantly greater amount of coronary artery obstruction. Although angina pectoris was an expression of pre-existing heart disease,[124] it resulted in the group with rupture from the combination of relatively little coronary disease and arterial hypertension. Therefore, angina was not a useful indication in this series of the extent of coronary obstruction or the likelihood of rupture.

Careful study of the selected microscopic sections in the ruptured hearts emphasized two facts: first, an acute myocardial infarct continues to change in extent for some time after its inception; and second, rupture ordinarily occurs through areas of more recent spread. Although the clinical picture indicates the *onset* of a myocardial infarction at a particular time, the entire infarct is not all of that same age. Infarction is a continuous and progressive process with the simultaneous repair of old areas, the development of fresh necrosis and the recovery of ischemic muscle. The occurrence of rupture through the more recently infarcted myocardium, which is continuously evolving, offers a basis for the wide time interval of three weeks after acute myocardial infarction during which rupture may occur.

Paradoxically, patients who die of rupture have even less evidence of serious heart disease, aside from hypertension, than patients who survive such an attack. Congestive failure and major, complicating pathologic states are both uncommon among patients with rupture. The catastrophe that abruptly terminates this relatively favorable picture may be anticipated in part by the ominous signs of antecedent and persistent hypertension, unusual effort and

the absence of previous infarction that would have caused the development of collateral circulation and fibrous tissue to buttress the walls of the heart. Patients such as those who develop rupture are often regarded as mild cases who are doing well and, therefore, do not need strict limitation of activities. It is in just this type of mild uncomplicated case in whom the blood pressure does not drop appreciably from the usual level and in whom rest is not rigorously enforced that rupture is likely to occur. The "sick coronary" with marked depression of the blood pressure level, with carefully supervised and prolonged bed rest because of complicating illnesses or gross congestive heart failure and with effective sedation for restlessness, dyspnea or recurrent chest pain is less likely to develop cardiac rupture and more prone to die of extensive infarction.

The hypothesis that a heightened intraventricular pressure is necessary to produce rupture of a necrotic myocardium is susceptible to experimental study in laboratory animals. Spontaneous cardiac rupture in animals[139–141] is rare. Cardiac rupture after experimental ligation of a coronary artery is also quite unusual.[142–163]

In a recent study involving injection of the coronary arteries and preparation of multiple microscopic sections,[9] acute myocardial infarction was produced by acute coronary artery ligation in 31 dogs. Although most of these hearts showed the pathologic substrate for rupture, myocardial rupture did not occur. These dogs were permitted the routine activities of the animal farm but were not exercised or subjected to special strain postoperatively. Attempts are now being undertaken in this laboratory to produce rupture by inducing hypertension and subjecting animals to other types of strain following acute coronary artery ligation.

Persistent hypotension secondary to acute myocardial infarction is generally accepted as an ominous event that is at times treated successfully with pressor agents.[164] Similarly, hypertension persisting during an acute infarct may eventually be considered a threat to life serious enough to justify the use of pharmacologic agents that depress the blood pressure to normotensive levels. Although such therapy cannot be recommended at this time, a precedent for its use may be found in the successful treatment of hypertensive crises and toxemias of pregnancy with the veratrum alkaloids.[165] For the present, rest and sedation in all patients with acute myocardial infarction will reduce cardiac work, perhaps lessen the extent of necrosis in ischemic areas and diminish the height of the intraventricular pressure. Avoidance of sudden or excessive exertion can be accomplished by cooperation of the patient, meticulous nursing care and conservative medical judgment. Since cardiac rupture accounts for almost one tenth of all deaths from acute myocardial infarction and occurs particularly in otherwise favorable cases, efforts to prevent rupture may increase appreciably the number of patients who make a good recovery from an initial myocardial infarction.

Summary and Conclusions

1. Twenty ruptured hearts were studied by a special technic consisting of injection and dissection of the coronary arteries and examination of multiple, carefully localized histologic sections of the myocardium. All 20 ruptures occurred through areas of acute myocardial infarction. A control series of 104 nonruptured hearts with acute infarction studied in the same way and the clinical records of 104 additional patients who survived an episode of acute myocardial infarction were examined for purposes of comparison. In addition, reports in the literature on cardiac rupture were reviewed.

2. The reported incidence of rupture among patients dying with acute myocardial infarction in general hospitals is approximately 9 per cent.

3. There is a uniform pathologic substrate common to hearts with spontaneous myocardial rupture. This substrate consists of an acute coronary artery occlusion and a recent myocardial infarction which is transmural, poorly supplied by collateral circulation and in which fibrosis is entirely absent in at least one area. These pathologic criteria select hearts which are totally unprotected by scar or anastomosis at the site of an acute myocardial infarction.

4. Concomitantly, there is significantly less

coronary artery occlusion and myocardial fibrosis among patients with acute infarction who die with rupture than among those who die without rupture.

5. There is likewise a "clinical profile" for the type of patient in whom rupture is most likely to occur. Rupture usually develops between the fourth and eleventh day of an acute myocardial infarction in a hypertensive patient with no previous history of old myocardial infarction or congestive failure. Persisting hypertension or excessive effort usually precede rupture.

6. Among patients with acute myocardial infarction rupture is relatively more common in women than men. This is due in part to the lesser extent of coronary disease and the greater incidence of hypertension among women.

7. Hearts that show the pathologic substrate for rupture may not perforate unless hypertension or excessive effort occurs during acute infarction; conversely, hypertension and excessive effort do not produce rupture if the appropriate cardiac pathology is absent.

8. Most acute myocardial infarctions change continuously in extent for some time after their inception, with simultaneous repair of old areas and involvement of new sites. The usual location of rupture through the more recently infarcted myocardium explains, in part, why rupture may occur almost any time during the first three weeks after the onset of necrosis.

9. Increased intraventricular pressure appears to be a critical factor in the development of cardiac rupture. Strenuous measures may, therefore, be justified to avoid or reduce arterial hypertension and effort in patients during acute myocardial infarction.

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The Action of SKF 688A (Phenoxyethyl Derivative of Dibenamine) upon Certain Functions of the Sympathetic Nervous System in Man

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A Dibenamine analogue was administered orally to five hypertensive and 10 normotensive subjects over periods from 14 to 21 days. Its adrenergic blocking effect was studied by observing blood pressure, pulse rate, skin temperature of the toes and the pupillary mechanism. Nasal congestion, weakness, listlessness, dizziness, drowsiness and palpitation were persistent sequelae of adrenergic blocking. The drug was found valuable for investigation of autonomous nervous system functions and may hold promise as a therapeutic agent for the treatment of arterial insufficiency and some types of hypertensive subjects.

SKF 688A (N-phenoxyisopropyl-N-benzyl-B-chlorethylamine hydrochloride) is a new adrenergic blocking agent. It is structurally and pharmacologically similar to Dibenamine but in contradistinction to Dibenamine, is tolerated orally. In animals, SKF 688A has been shown to be 10 times as potent as Dibenamine intravenously and twice as active by mouth.[1]

The pharmacologic actions of Dibenamine have been described by Nickerson, Goodman, Nomaguchi[2] and others.[3–6] Following intravenous injection of Dibenamine in man, a decrease in systolic and diastolic blood pressure was noted in some,[3] and orthostatic hypotension and marked pupillary contraction were noted in all patients.[4] All authors were able to demonstrate increased peripheral blood flow in patients with peripheral vascular disease. Although Haimovici[4] reported orthostatic hypotension in all patients tested, significant change in the resting blood pressure occurred only when hypertension was present. A marked reduction in both systolic and diastolic blood pressure was produced in patients with "benign" hypertension, but only a slight decrease occurred in those with "malignant" hypertension. Myers and co-workers[6] noted temporary symptomatic remission in 7 of 10 patients with hypertensive encephalopathy. More recently, intravenous injection of Dibenamine has been used to reduce intraocular pressure in glaucoma when other medical agents were ineffective.[7, 8] In general, its use has been limited by the severe systemic manifestations and the necessity for intravenous administration.

Preliminary studies with 688A in human subjects[9] have shown that postural hypotension, miosis, and vasodilatation follow the use of this drug by mouth as well as intravenously. Other effects reported were faintness, weakness, fatigue, diarrhea, drowsiness, headache, nasal congestion and blurred vision.

Moser and co-workers[10] administered 688A to 19 patients. Most cases developed postural tachycardia, miosis and nasal congestion. Extreme postural hypotension developed in one case. The blood pressure fell to normal or slightly above in six of nine hypertensive patients under the age of 50. The fall in blood pressure was maintained as long as the drug was continued, but rose within 36 to 72 hours after the drug had been stopped.

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Methods and Material

The plan of the present study was to follow the effects of the drug over a prolonged period of administration (just as the drug would be given clinically) rather than to measure the vasodilator effects for only a few hours following a single dose. From this type of study it would also become clear whether repeated doses continued to elicit the original response.

Fifteen patients were studied before, during, and after administration of 688A in doses of 40 mg. every eight hours (table 1). Twelve-lead electrocardiograms were taken on 12 of them before and during administration of the drug. Blood pressure and pulse rate were recorded daily in both the sitting and standing positions on all patients.

Skin temperatures were recorded in 10 of the patients during a control period and while the drug was being administered. Temperatures were recorded every 27 seconds for 180 minutes on a Leeds and Northrup speedomax in a constant temperature room at 19.5 ± 1 C. and 50 ± 5 per cent humidity. All observations were made following abstinence from food and tobacco for at least four hours at approximately the same time of day with one exception (JW). Likewise an interval of about five hours after the last dose of the drug preceded each period of observation.

An ophthalmologic survey was carried out on each patient. Intraocular tensions, pupillary responses, measurements of accomodation, and visual acuity determinations were recorded throughout the three periods of the experiment.

All tensions were measured with the same Schiotz tonometer, with the patient at the same reclining

Table 1.—*Summary of Clinical Data of Patients Studied and Comparison of Their Resting Blood Pressures before and during Administration of SKF-688A*

Pt.	Age	Sex	Diagnosis	BUN	EKG	Control BP	BP under 688A*	Days on 688A†
JK	64	M	Hypothyroid, cataracts, generalized arteriosclerosis	18.5	Normal	150/58	150/60	14
MR	73	M	Diabetes mellitus, cataracts, arteriosclerosis obliterans	20.8	Myocardial damage	132/94	130/80	19
VR	62	M	Arteriosclerotic ht. disease; arteriosclerosis obliterans	20.8	Atypical RBBB	150/90	125/65	17 and 15‡
RA	50	M	Portal cirrhosis, hypertension, arteriosclerosis obliterans	10.1	Left axis deviation	160/90	160/80	9
DF	46	M	Hypertensive cardiovascular disease	38.6	Left axis deviation	230/140	170/130	3
RS	60	M	Hypertension, right hemiplegia	18.2	Left axis deviation	220/130	190/120	12
WB	29	M	Hypertension, subacute nephritis	21.5	Normal	145/105	130/90	16
JC	46	M	Arteriosclerotic heart disease, nephrosclerosis	68.0	Auricular fibrillation, LBBB	160/80	160/80	5
AG	40	F	Polyneuritis	10.5	Normal	110/70	116/74	16
CH	13	M	Rheumatic fever	15.5	Normal	110/80	110/80	16
JR	60	M	Arteriosclerotic heart disease, duod. ulcer, left hemiplegia	10.6	Right bundle branch block	160/80	155/80	16
FA	66	M	Pulmonary fibrosis, bronchiectasis	12.5	Left axis deviation	110/60	80/56	1
JF	52	F	Portal cirrhosis	13.0	Normal	124/80	130/80	15
YL	48	F	Hypertension, malignant	19.5	Left axis deviation	260/150	230/130	11
JW	41	M	Hypertensive cardiovascular disease	20.0	Sinus tachycardia, myocardial involvement	175/98	130/80	7

* The readings listed under 688A are the lowest recorded during the experimental period.

† Dosage of SKF-688A was 120 mg. per day.

‡ This patient received 688A for two periods, one for 17 days and the second, for 15 days.

angle, and at the same hour each day. Pupillary measurements were recorded under standard lighting conditions. Tearing was evaluated by means of the Schirmer test, and the Hertel Exophthalmometer was used to ascertain any change in position of the globe. Tests for accomodation were performed (utilizing the Duane Card) following adequate correction of refractive error. In addition, concurrent changes in the refractive state were sought. Ten per cent Neosynephrine (Winthrop-Stearns) was the drug used topically to mimic sympathetic stimulation of the iris. Reactions to local instillation of 4 per cent cocaine hydrochloride, 1 per cent Paredrine hydrobromide (SKF), 5 per cent homatropine hydrobromide, 0.25 per cent eserine salicylate, and 2 per cent pilocarpine hydrochloride were also studied.

Results

The effects obtained by oral administration of SKF 688A were, in general, like those obtained with intravenous Dibenamine. One patient (VR) was treated with 688A twice, with an eight-week interval between. In five patients the drug was stopped after periods of administration ranging from 1 to 11 days because of various "toxic" reactions. Ten patients were maintained on it for periods of 14 to 21 days.

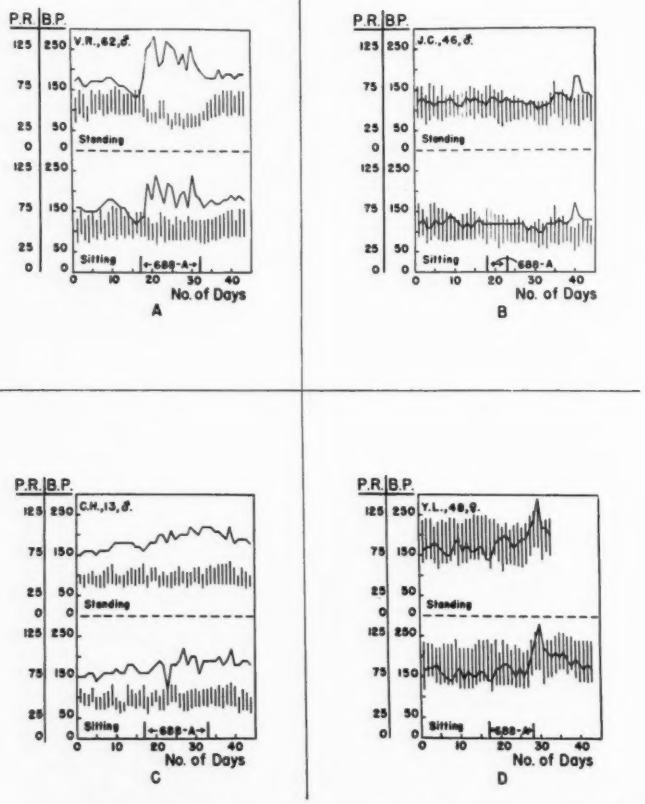

FIG. 1. Four examples of the response of blood pressure and pulse rate to administration of SKF 688A are shown. *A*. Marked response in both pulse rate and blood pressure. *B*. Relatively little response of either. *C*. Lack of response in blood pressure with moderate rise in pulse rate. *D*. Little response in blood pressure with a curious rise in rate at the end of administration of the drug.

Circulatory Effects

The resting blood pressure was significantly reduced in seven patients and was unchanged

in eight (table 1). Postural hypotension was produced in eight patients. Four did not have any changes in blood pressure on standing, and in three, observations could not be made in the erect position.

In seven patients there was an increase in pulse rate during the drug period. This tachycardia was marked in five. It was still more marked in the erect position. Even on rest it persisted for about a week after the drug was stopped. In one patient (YL) tachycardia began just at the end of the period of administration of the drug. The tachycardia was generally more marked on standing. Figure 1 illustrates the different types of response of blood pressure and pulse rate.

TABLE 2.—*Comparison of Surface Temperatures of Fingers and Toes of 10 Patients before and during Administration of SKF 688A*

Pt.	Great Toes (Average)			Middle Fingers (Average)		
	Control	688A	Change*	Control	688A	Change*
JK	21.6	29.8	8.2	21.2	23.7	2.5
MR	24.1	26.7	2.6	21.1	21.0	−0.1
VR	23.9	21.5	7.6	23.6	28.7	5.1
WB	19.1	20.1	1.0	19.4	21.4	2.0
JC	20.7	29.2	8.5	20.1	21.5	1.5
AG	19.2	20.9	1.7	19.2	19.0	−0.2
CH	22.4	26.1	3.7	33.6	32.0	−1.4
JF	19.5	29.0	9.5	35.2	34.0	−1.2
YC	21.2	26.0	4.8	32.5	33.5	1.0
JW	31.0	33.8	2.8	33.3	34.0	0.7

The temperatures given are the temperatures at the end of a 180 minute period of adaptation in the constant temperature room at 21 C., 50 per cent humidity. Since the differences between the temperature of the correspondent digits of the two sides were small, the average of the two is given.

* A rise is indicated, unless the sign is minus.

The development of auricular fibrillation was noted in JW after seven days on 688A. When the drug was stopped, the electrocardiogram showed auricular flutter with 2:1 block which had become a 4:1 block two days later and then sinus tachycardia. The day previous to the development of the auricular fibrillation he had received 4 cc. of Mercuhydrin and 1 Gm. of aminophylline intravenously with the loss of 12 pounds. Subsequent to later intravenous injections of aminophylline, transient episodes of auricular fibrillation occurred. The role, if any, which SKF 688A played in producing this arrhythmia, is very dubious.

The temperature of the toes was significantly higher in all patients while taking the drug (table 2 and fig. 2). In two patients (MR and VR) the elevation of temperature of the toes persisted for 17 and 13 days, respectively, after the drug had been discontinued. The response in temperature of the fingertips was erratic and inconclusive (table 2 and fig. 3).

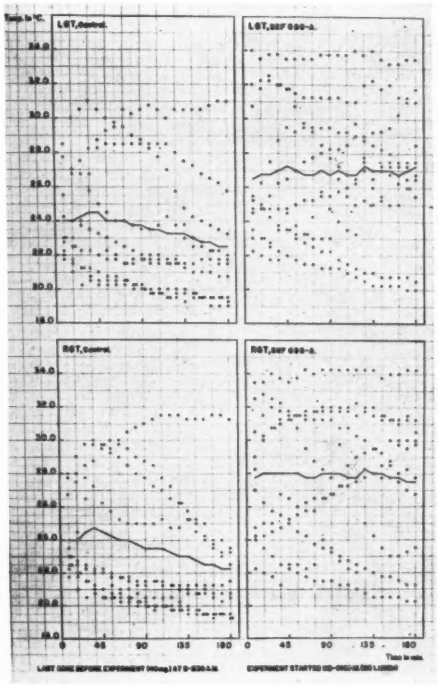

FIG. 2. Skin temperature response to SKF 688A in both great toes of 10 subjects. The solid lines connect mean values.

Ocular Effects

The outstanding ophthalmologic findings were those related to pupillary response. An inability of the iris to dilate in darkness developed as early as 24 hours after SKF 688A had been started and was present in all cases after 96 hours. The diameter of the pupils was the same in a normally lighted room after medication as before (2.5 to 3 mm.). The pupil

did, nevertheless, continue to respond to a very bright light, to convergence and to eserine and pilocarpine by further contraction. The pupils also lost their ability to dilate with 10 per cent Neosynephrine and this loss persisted for a variable period of time (from less than 24 hours to nearly a week) after withdrawal of the drug. Likewise, instillation of 4 per cent

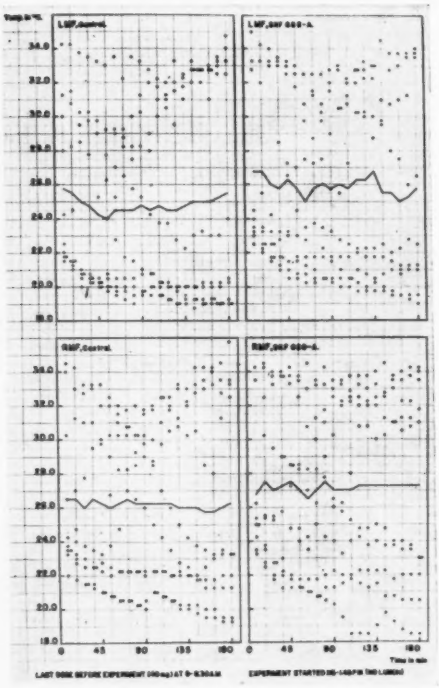

FIG. 3. Skin temperature response to SKF 688A in both middle fingers of 10 subjects. The solid lines connect mean values.

cocaine failed to cause dilation. Five per cent homatropine hydrobromide did, however, cause some pupillary dilation.

After SKF 688A had been discontinued, normal response to darkness and Neosynephrine returned in some instances within 24 hours and all individuals responded fully after seven days. There was no direct correlation between total dosage of SKF 688A and the rapidity of recovery of the ability of the iris to dilate after stopping the drug.

Significant changes were not noted in intraocular tension, appearance of fundi, Schirmer tests, accommodative findings, refractive errors, position of the globes, palpebral fissure measurements, and extraocular muscle functions.

Effects on Other Organs

All patients noted nasal congestion within 48 hours, and in two, this was accompanied by epistaxis. Weakness and listlessness occurred in five patients. Four complained of headaches and three developed vomiting, with diarrhea in one. Three complained of dizziness, which was especially marked in one. Three patients noted palpitation and three were noted to be excessively drowsy. A short resume of one case is presented since the development of the pneumonia may be considered to have been due to congestion of the mucous membranes of the respiratory tract even though the total dose was exceedingly small.

One patient, a 65 year old white man with bronchiectasis, pulmonary fibrosis and emphysema, was given 120 mg. of 688A on the twenty-third day of hospital observation. During that day it was noted that his temperature was slightly elevated. The following day he became dyspneic and drowsy, but could be easily aroused. His blood pressure was 80/56 as compared to his normal of 110/60. His temperature was 100 F. and pulse was 120. The breath sounds were diminished over the right lung and there was bronchial breathing at the left base. X-ray films showed an infiltration in the left mid and lower lung field and in the right lower lung adjacent to the heart. An electrocardiogram showed a sinus tachycardia with some decrease in amplitude of the T waves. The 688A was stopped after a total dose of only 120 mg. and he was given an infusion of 1000 cc. of normal saline. His blood pressure rose to 96/60 following the infusion and remained at normal levels for the next two days. He was treated with antibiotics and appeared improved despite the fact that his pneumonia spread to the right lung base. Four days later he expired with a massive pulmonary hemorrhage.

DISCUSSION

In doses of 120 mg. daily by mouth, 688A is a powerful adrenergic blocking agent. In fact, a smaller dose may be effective in many subjects and cause fewer side effects. The effects were evident within 24 hours; nasal congestion appeared to be the first clinical sign of adrenergic blocking. The drug is long acting and effects

on the peripheral circulation were observed as long as 13 and 17 days and on pupillary response, as long as seven days after the drug had been stopped. Prolonged action had also been noted with Dibenamine. Brodie and associates[11] have suggested that prompt localization of the drug in body fat with subsequent slow release may be responsible for this phenomenon. Clinically, one would expect that obese people would have the most prolonged response to the drug. The range of obesity was not sufficiently great in our group of patients to examine this point.

Correlation between response in blood pressure and in pulse rate was not demonstrable. Correlation between drop in blood pressure and rise in skin temperature of the toes was likewise unclear but tended to be negative. Of 10 subjects, seven had a toe temperature increase of 3 degrees or more. Only one of these experienced a drop in blood pressure, while two of the three who had an increase of less than 3 degrees had a drop in blood pressure. The explanation for the tachycardia after adrenergic blockade is not clear; it has been noted with other similar-acting drugs.[12, 13, 14]

Electrocardiographic changes secondary to 688A were minimal and in general explained by increase in rate.

The responses of the fingertips were variable and confirm the fact that the fingers are unsatisfactory indicators of vasodilator effect. Of a total of five subjects with obliterating arteriosclerosis, two reported here and three tested previously, only one had drop in blood pressure, while all of them had increase in temperature of the toes.

All response of the dilator muscle of the iris to sympathetic innervation was lost under the influence of SKF 688A. The position taken by the iris is due to the tonus of the sphincter muscle, and the fact that miosis did not occur leads to the conclusion that very little sympathetic stimulation of the part is present under static conditions. That the sphincter is not in spasm is demonstrated by the size of the pupil, its reaction to light, as well as to pilocarpine and eserine. It is further confirmed by the fact that when the sphincter tonus is removed by the use of homatropine (which blocks parasympathetic response) the pupil assumes an intermediary size.

The fact that 688A had no influence on normal intraocular tension does not preclude its trial under abnormal conditions of ocular pressure. The interplay between sympathetic and parasympathetic control has been lately under serious consideration as a possible etiologic factor in glaucoma.[15]

Four patients complained of slight blurring of distant vision coincident with objective pupillary response to the drug. On examination there was no objective diminution to visual acuity nor was there a demonstrable change in accomodation. As a matter of fact, visual acuity was actually increased; the patients were able to see a blurred line on the chart where they had seen none at all before administration of the drug. This is obviously due to the maintenance of a small pupil in a dark room.

Nasal congestion, weakness and listlessness, dizziness, drowsiness and palpitation which were observed are more or less to be expected as direct physiologic sequelae of adrenergic blocking. It is interesting that all these effects had a great tendency to appear delayed and to outlast considerably the period of drug administration. In contrast to this, nausea and vomiting tended to disappear after the first two or three days, while administration of the drug was continued.

SKF 688A will undoubtedly be of value in physiologic studies concerning the function of the autonomous nervous system. It may turn out to be of therapeutic value in glaucoma, in occlusive arterial disease of the extremities, and possibly in some types of hypertension. The drug is probably contraindicated in patients with chronic pulmonary disease, because of the congestion of the mucous membranes of the respiratory passages including those of the bronchial tree.

Summary

1. A new adrenergic blocking agent, SKF 688A (N-phenoxyisopropyl-N-benzyl-B-chlorethylamine hydrochloride), was given to 15 patients in oral doses of 40 mg. every eight hours for periods from 14 to 21 days. Five of the patients were hypertensives.

2. The resting blood pressure was lowered in seven patients. Four of these had hypertension.

3. Five patients showed marked increase in pulse rate, which outlasted the administration of the drug by about a week; two had slight increase in pulse rate during the drug period; one had marked increase in pulse rate, starting at the end of the drug period; seven had no significant increase in pulse rate.

4. All patients showed significant rises in skin temperature of both big toes under action of the drug.

5. Impairment of pupilary dilator mechanism was observed in all patients within 72 hours after beginning of administration of the drug. The type of impairment is described in detail.

6. Nasal congestion, weakness and listlessness, dizziness, drowsiness, palpitation are sequelae of adrenergic blocking and are persistent. Nausea and vomiting tend to disappear after the first two or three days and are probably not due to the adrenergic blocking action.

7. Adrenergic blocking agents may aggravate the symptoms of patients with pathology of the respiratory tract.

8. SKF 688A is a valuable drug for investigation of autonomous nervous system functions and deserves thorough study as a therapeutic agent for the treatment of arterial insufficiency and some types of hypertensive subjects.

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Observations on the Fate of Ingested Cholesterol in Man

By M. W. Biggs, M.D., D. Kritchevsky, Ph.D., D. Colman, A.B., J. W. Gofman, M.D., Ph.D., H. B. Jones, Ph.D., F. T. Lindgren, B.S., G. Hyde, M.D., and T. P. Lyon, M.D.

Tritium-labeled cholesterol has been used to study several aspects of exogenous cholesterol metabolism in man. The rate and magnitude of the appearance of ingested cholesterol in the various blood compartments has been followed. Fecal excretion of the labeling material was measured. Cholesterol of dietary origin was demonstrated in a human atherosclerotic aorta.

THE PART played by the lipid content of the diet in the development of atherosclerosis is a controversial point among investigators of atherosclerosis and associated diseases. Some investigators would implicate the fat and cholesterol content of the diet as a major contributing factor while others deem it of little or no importance. The rightful positioning of dietary factors in the pathologic sequence of events leading to the development of atherosclerosis must await a more complete knowledge of some of the fundamental aspects of lipid metabolism. The present report deals primarily with the absorption and turnover of ingested cholesterol in the various compartments of the blood in four patients, all of whom undoubtedly had some degree of atherosclerosis. One patient had previously had a typical myocardial infarction, the second had chronic glomerulonephritis with hypertension, the third had xanthoma tendinosum of many years duration, and the fourth experienced a cerebrovascular accident and came to autopsy.

Each of these patients was given a single oral dose of tritium-labeled cholesterol by mouth. The appearance of this labeled compound in the total serum cholesterol, free serum cholesterol, and red blood cell cholesterol was followed for from two to six weeks. Examinations of the feces were done in two cases.

Methods

Tritium (H^3) labeled cholesterol has been used as the tracer compound in these studies. This choice of labeling material stems primarily from the fact that tritium in the doses required does not involve an appreciable radiation hazard, hence is safe for human experimentation. The tritium-labeled cholesterol was prepared by a catalyzed exchange reaction according to the method of Bloch and Rittenberg[1, 2] and the specific activity of the tritium-cholesterol so prepared varied from 0.48 to 1.07 mc. of tritium per gram of cholesterol in different preparations. This compound so prepared contains 46 per cent of the label in the vicinity of the Δ^5-3-hydroxyl system and 54 per cent in the isopropyl group of the side chain according to Fukushima and Gallagher.[3, 4] It has been shown repeatedly that this tritium label occupies stable positions in that there is no reduction of specific activity on refluxing this tritium-cholesterol in 30 per cent potassium hydroxide in 50 per cent alcohol for 12 hours. Recent work in this laboratory employing cholesterol doubly labeled with carbon-14 and tritium for feeding experiments in rabbits indicates that tritium-labeled cholesterol is a suitable tracer compound for the investigation of many aspects of in vivo cholesterol metabolism.[5]

The patients reported here each received an oral dose of tritium-cholesterol dissolved in warm Wesson oil emulsified into whole milk, excepting patient 2, who received the tritium-cholesterol in the crystalline form dispersed in milk.

The various blood and tissue cholesterol samples were all isolated as the digitonide; these samples in turn were combusted and the water obtained allowed to react with lithium aluminum hydride to generate hydrogen. The hydrogen-tritium mixture was assayed in an ionization chamber.[6] The total tritium content of the feces was determined by burning a sample of whole, wet feces and assaying the water obtained as above.

Experimental Data

Patient 1 was a 69 year old woman who five years previously had experienced a sudden collapse associated with crushing chest pain. Electrocardiograms showed classic changes of a posterior myocardial infarction. Since this episode the patient has been on

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limited activity and has felt fairly well except for occasional episodes of chest pain and dypsnea usually associated with excitement or overexertion. At the time of this study the patient felt well, her appetite was good, her weight was stationary, and bowel function was regarded as normal.

Fluoroscopic examination of the chest showed no evidence of cardiac enlargement. The pulse was regular at 76 and the heart sounds were not remarkable. The blood pressure was 140/95. The abdomen was negative and there was no edema.

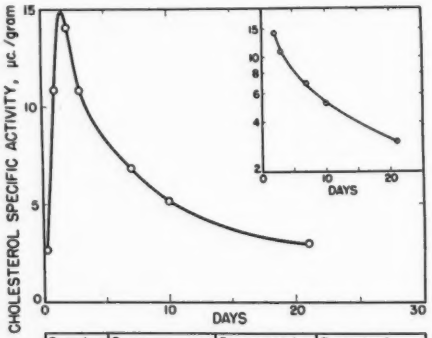
Laboratory examination of the urine was negative. The red blood count was 5.0 million, hemoglobin was 14.0 Gm., white blood count was 6,000. The electrocardiogram showed signs of a healed posterior myocardial infarction.

This patient was given 1.55 Gm. of tritium-labeled cholesterol (specific activity equal to 0.480 mc. of tritium per gram of cholesterol) by mouth. The cholesterol was dissolved in 10 cc. of warm Wesson oil and emulsified into a glass of whole milk. Studies on the specific activity of the total serum cholesterol were done over a period of three weeks. The results are tabulated in figure 1.

An ultracentrifugal analysis of this patient's serum lipoproteins at the beginning of the experiment according to the method of Gofman[7] showed the following concentrations*: S_f 12–20 = 114m g. per 100 cc.; S_f 20–100 = 428 mg. per 100 cc. The analytic ultracentrifuge plate is included in figure 5.

A serum sample obtained 24 hours after the administration of the tritium-cholesterol dose was submitted to ultracentrifugal partition according to the method of Lindgren.[8] In this way the lipoproteins of the serum were separated into four fractions according to their Svedberg flotation rates, that is, S_f 3–7, S_f 10–13, S_f 17 and S_f 20+.† The specific activity of the total cholesterol of each fraction was determined. The results follow: S_f 3–7 cholesterol S. A. = 11.0 μc. per gram; S_f 10–13 cholesterol S. A. = 11.0 μc. per gram; S_f 17 cholesterol S. A. = 10.3 μc. per gram; and S_f 20+ cholesterol S. A. = 10.9 μc. per gram. The specific activity of the total serum cholesterol determined prior to ultracentrifugal treatment was 10.9 μc. per gram.

A body water sample obtained on day two by freeze drying a serum sample did not show measurable activity. The sensitivity of the counting equipment is such that 1.0×10^{-2} μc. of tritium per gram of water can be detected.



Sample	Serum cholesterol values, mg.%		Serum total cholesterol specific activities, μc./gram	Percent of ingested T-cholesterol found in total blood*
	free	total		
6 hours	64	225	2.7	2.4
1 day	57	199	10.9	9.7
2 days	54	183	14.1	12.6
3 days	53	181	10.9	9.7
7 days	60	179	6.9	6.2
10 days	58	199	5.2	4.6
21 days	54	207	3.0	2.6

FIG. 1.—The appearance of tritium-cholesterol in the blood of patient 1 following ingestion of 1.55 Gm. of cholesterol, containing 0.744 mc. of tritium. The insert is a semilog plot of the descending specific activity values.

* Approximated using a total blood volume equal to 67 cc. per kilogram of body weight.

Patient 2 was a 41 year old male who had chronic glomerulonephritis with hypertension of unknown duration. Two years prior to this study he first noticed backache and was found to have albuminuria and an elevated blood pressure. These initial signs were soon followed by cramping of the muscles of the hands and subjective swelling of the face. Within three months frank edema of the hands and ankles developed associated with nocturia.

At the time of this study the patient was ambulatory and manifested no objective edema. There was marked weakness on moderate exertion. Occipital headaches were frequent and subjective edema of the face was present each morning on awakening.

* The molecules are identified by their characteristic flotation rates under specified ultracentrifugal conditions. Units are Svedbergs of flotation (S_f). One S_f unit equals a migration rate of 10^{-13} cm./sec./dyne./Gm. at 26 C. in a medium of NaCl solution of density 1.063.

† The fraction designated S_f 20+ includes all the lipoprotein molecules with Svedberg flotation rates of 20 units (S_f 20) and greater, up to and including chylomicrons.

Vision was failing steadily. The appetite was good and bowel function was regarded as normal.

Fluoroscopic examination of the heart showed some left ventricular enlargement. The pulse was regular at 75 and the blood pressure was 230/135. There was grade III hypertensive retinopathy. There was no objective edema or ascites, and examination of the abdomen was negative.

Clinical laboratory studies showed a red cell count of 2.80 million, hemoglobin of 9.3 Gm., and a white cell count of 9,700. The urine had a specific gravity of 1.015 and showed 4+ albumin, an occasional white blood cell, a rare red blood cell and an occasional coarse granular and hyaline cast. The nonprotein nitrogen was 79 mg per cent; blood creatin 6.7 mg. per 100 cc. The total serum proteins were 7.7 mg. per 100 cc. with an albumin-globulin ratio of 0.35. The basal metabolic rate was −3. A fasting serum calcium was 4.7 mEq. per liter. An electrocardiogram was interpreted as a normal tracing.

This patient ingested 0.856 Gm. of tritium-cholesterol (specific activity equal to 0.853 mc. per gram) emulsified as crystalline cholesterol into 250 cc. of whole milk in a Waring blender. Following this single meal of 730 μc. of tritium-cholesterol in crystalline form the patient was placed on a 2400 calorie diet which contained 100 Gm. of protein and 80 to 90 Gm. of fat. Salt intake was limited to 2 to 3 Gm. per day.

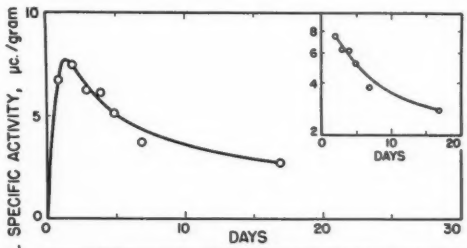
The results of studies on the blood cholesterol are tabulated in figure 2. Studies on the total tritium content of the feces are contained in table 1.

The feces obtained on day 2 containing 169 μc. of tritium was lyophylized and the dried residue extracted first with 95 per cent alcohol and then with ether. The extracts were combined and saponified with 20 per cent potassium hydroxide in 50 per cent alcohol. The crude nonsaponifiable material (1.34 Gm.) contained 147 μc. of tritium and had a specific activity of 110 μc. per gram.

An ultracentrifugal analysis of this patient's serum lipoprotein structure showed: S_f 12–20 = 97 mg. per 100 cc.; S_f 20–100 = 168 mg. per 100 cc. The analytic ultracentrifuge plate is included in figure 5.

Patient 3 was a 51 year old woman who has had known xanthomata in the tendons at the ankles and elbows since the age of 20. Two years prior to this study she first began to experience postprandial distress and tightening across the anterior chest on exertion. Eighteen months ago there had been a frank myocardial infarction requiring one month's hospitalization. Since this episode she supposedly had been on a "low fat" diet but continued to experience angina pectoris with pain radiating into the left arm and neck on moderate exertion. At the time of this experiment the patient was ambulatory and able to support herself doing sedentary work.

Examination showed numerous tendinous xanthomata at the ankles, elbows and on the feet and hands. There were also xanthelasmata. The heart



Sample	Serum cholesterol values, mg. %		Cholesterol specific activities, μc./gram			Percent of ingested T-cholesterol found in total blood*
			Serum		R.B.C.	
	free	total	free	total		
1 day	73	273	7.7	6.8	5.0	7.8
2 days	74	257	7.3	7.5	7.6	9.3
3 days	76	288	6.0	6.3	7.4	8.2
4 days	79	277	6.2	6.2	6.0	7.6
5 days	78	268	6.0	5.2	5.8	6.7
7 days	75	258	3.9	3.8	3.9	4.7
17 days	76	266	–	2.8	2.7	3.4

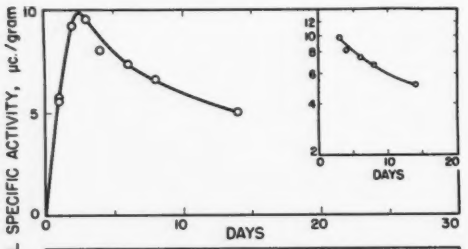
FIG. 2.—The appearance of tritium-cholesterol in the blood of patient 2 following the ingestion of 0.856 Gm. of cholesterol containing 0.730 mc. of tritium. The insert is a semilog plot of descending specific activity values.

* Approximated using a total plasma volume of 39 cc. per kilogram body weight, and a total red cell volume of 28 cc. per kilogram body weight.

TABLE 1.—*Tritium Content of the Feces Following the Oral Administration of 730 μc. of Crystalline Tritium-Cholesterol in Patient 2*

Sample	Stool Wet Weight	Tritium Content	Administered Tritium-Cholesterol
	Gm.	*μc.*	*%*
Day 1	132	261	25.8
Day 2	148	169	23.2
Day 3	207	123	16.8
Day 4	184	46	6.3
Day 5	129	23	3.2
Day 6	234	10	1.4
Day 7	147	5	0.7
Totals		637	87.4
Day 17	100	1.5	0 21

sounds were normal and the pulse was regular at 70. The blood pressure was 110/70. Funduscopic examination showed some tortuosity and silver wiring of the retinal vessels. The rest of the examination was negative.



Sample	Serum cholesterol values, mg. %		Cholesterol specific activities, μc./gram			Percent of ingested T-cholesterol found in total blood*
			Serum		R.B.C.	
	free	total	free	total		
1 day	144	548	7.8	5.8	4.2	12.3
			7.7	5.6		
2 days	155	562	10.1	9.3	9.5	19.2
3 days	145	554	9.7	9.6	9.4	19.3
4 days	143	504	8.1	8.1	8.0	15.2
6 days	154	580	6.8	7.4	–	–
8 days	140	546	5.7	6.7	–	–
14 days	144	553	4.2	5.1	4.5	10.0

FIG. 3.—The appearance of tritium-cholesterol in the blood of patient 3 following the ingestion of 0.688 Gm. of cholesterol containing 0.736 mc. of tritium. The insert is a semilog plot of descending specific activity values.

* Approximated using a total plasma volume of 39 cc. per kilogram body weight, and a total red cell volume of 28 cc. per kilogram body weight.

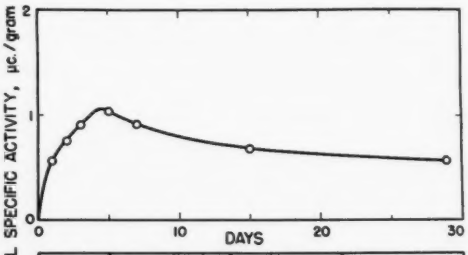
TABLE 2.—*Tritium Content of the Feces Following the Oral Administration of 736 μc. of Tritium-Cholesterol in Patient 3*

Sample	Stool Wet Weight	Tritium Content	Administered Tritium-cholesterol
	Gm.	*μc.*	%
Day 1	111	0.5	0.1
Day 2	99	26	3.5
Day 3	122	291	39.5
Day 4	94	67	9.1
Day 5	105	30	4.1
Day 6	none	—	—
Day 7	116	4	0.6
Totals		418.5	56.9

Laboratory studies showed a red cell count of 3.10 million, a hemoglobin of 10.0 Gm., and a white blood count of 8,500. The urine examination was normal. The electrocardiogram showed evidence of past myocardial damage.

The patient was given 0.688 Gm. of tritium-labeled cholesterol (specific activity equal to 1.07 mc. per gram) by mouth. This 0.736 mc. of tritium-cholesterol was dissolved in 10 cc. of warm Wesson oil and emulsified into milk. Following this fatty meal the patient was placed on a hospital diet adequate in calories and vitamins but limited to 20 Gm. of fat. The patient continued on this diet throughout the study.

The results of the studies on the blood are given in figure 3. The stool data are contained in table 2.



Sample	Serum cholesterol values, mg. %		Serum total cholesterol specific activities, μc./gram	Percent of ingested T-cholesterol found in total blood*
	free	total		
1 day	55	244	0.57	1.1
2 days	61	229	0.76	1.4
3 days	63	213	0.91	1.5
5 days	69	197	1.05	1.6
7 days	53	184	0.92	1.3
15 days	49	180	0.69	1.0
29 days	45	165	0.58	0.8

FIG. 4.—The appearance of tritium-cholesterol in the blood of patient 4 following ingestion of 0.650 Gm. of cholesterol containing 0.696 mc. of tritium.

* Approximated using a total blood volume equal to 67 cc. per kilogram of body weight.

An ultracentrifugal analysis of this patient's lipoprotein structure showed: S_f 5–10 = 870 mg. per 100 cc.; S_f 12–20 = 187 mg. per 100 cc.; S_f 20–100 = 112 mg. per 100 cc. The analytic ultracentrifuge plate is included in figure 5.

Patient 4 was a 62 year old man who experienced a massive cerebrovascular accident and was brought to the hospital unconscious. Details of his history prior to this fatal episode are lacking. At the time the tritium-cholesterol was given the patient was comatose. The neck was stiff and there was a spastic paralysis of the right arm and leg. Examination of the lungs revealed inspiratory rales at both lung bases. The blood pressure was 130/90. The cardiac rhythm was regular at 80, and there was a systolic

murmur in the aortic region. The patient was incontinent of urine and feces.

For eight days prior to the beginning of this study the patient had received nothing by mouth; saline and glucose clyses had been transient period beginning at about three weeks small oral liquid feedings were given. Forty-three days after the tritium-cholesterol was given the patient died and an autopsy was done.

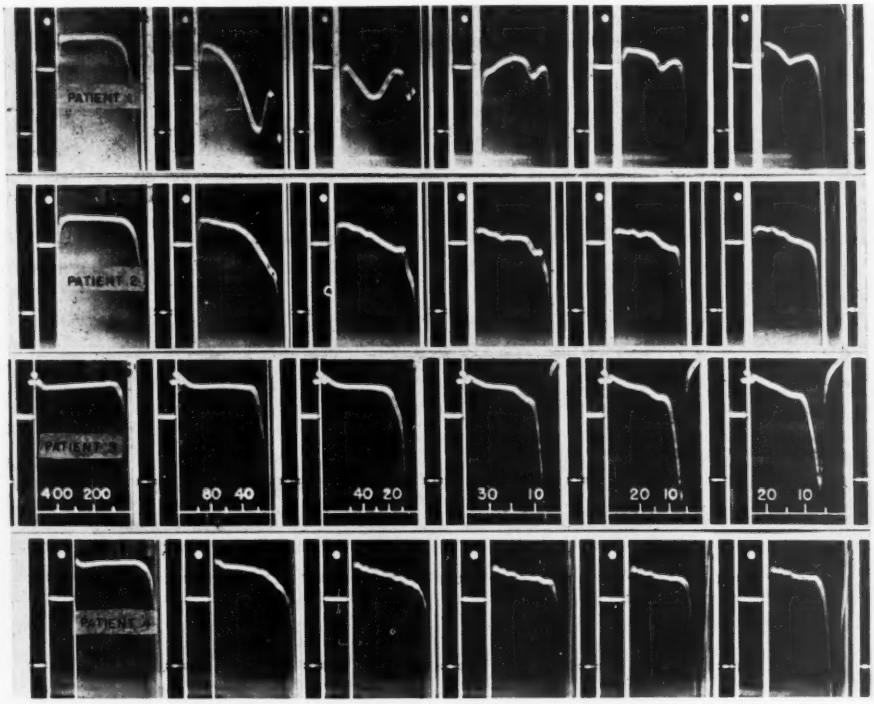


FIG. 5.—Ultracentrifugal flotation patterns showing the low density lipoprotein spectrum present in the four patients studied for response to oral ingestion of H^3-labeled cholesterol. Runs are made at 52,640 revolutions per minute with photographs taken at 0, 6, 12, 22, 30, 38 minutes after full rotor speed is reached.[7] The plate of patient 3 is ruled with an S_f rate grid, so that the flotation rate of any lipoprotein appearing in each frame can be immediately determined. This grid also applies to corresponding frames in the plates of patients 1, 2, 4.

All sera are concentrated five-fold prior to analytic ultracentrifugation, except for that of patient 3 which is one-fold.

The S_f 12–20 lipoprotein is elevated in all patients. The S_f 20–100 lipoprotein level is elevated in all patients except patient 3.

administered daily. The patient received 0.650 Gm. of tritium-cholesterol (specific activity equal to 1.07 mc. of tritium per gram) by stomach tube. This 0.696 mc. of tritium-cholesterol was dissolved in 15 cc. of Wesson oil and emulsified into 250 cc. of whole milk. Following this cholesterol feeding the patient received nothing by mouth for three weeks, all nourishment being administered by injection. For a

The immediate cause of death was an extensive bilateral hypostatic bronchopneumonia. Examination of the cerebral vessels showed marked atherosclerotic changes and in the left parietal region there was a large area of encephalomalacia secondary to thrombosis of the left middle cerebral artery. The aorta which was saved for chemical examination was so extensively involved with atherosclerosis that

no areas of "normal" aorta were visible. Many of the plaques were ulcerated and calcified. The coronary vessels showed calcification and numerous areas of atherosclerotic stenosis.

The total serum cholesterol specific activities are recorded in figure 4. The total liver cholesterol was found to have a specific activity of 0.30 μc. per gram. The thickened intima of the aorta was carefully separated from the adventitia and much of the media and consisted of 36.0 Gm. of tissue. From this source, 1.31 Gm. of cholesterol were separated. This cholesterol separated as the digitonide had a specific activity of 0.03 μc. per gram.

An ultracentrifugal analysis of this patient's serum lipoprotein structure eight days following the cerebrovascular accident showed: S_f 12–20 = 65.4 mg. per 100 cc.; S_f 20–100 = 82.3 mg. per 100 cc. The analytic ultracentrifuge plate is included in figure 5.

Discussion

Following a single tracer cholesterol meal to man the serum cholesterol specific activity increased rapidly during the first day and reached a maximum specific activity in from 36 to 72 hours as in figures 1 to 3. Thus cholesterol absorption in man appears to be a slow process normally continuing over a period of approximately two to three days. Examination of the feces of patients 2 and 3 showed continued excretion of large amounts of tracer material over a period of several days entirely consistent with such a period of cholesterol absorption.

There can be no doubt that dietary cholesterol plays a role in serum cholesterol metabolism for appreciable amounts of dietary tracer cholesterol were readily demonstrable in the serum of patients 1, 2, and 3 throughout the study periods. Two days after the tritium-cholesterol meal approximately 12.5 per cent of the 1.55 Gm. of cholesterol fed to patient 1 existed in the circulating blood; about 9.3 per cent of the administered dose was demonstrable in patient 2; and about 19.2 per cent of the dose was found in the blood of patient 3.

It has been observed repeatedly in hypercholesterolemic rabbits that during the first 72 hours following a single tritium-cholesterol meal the specific activity of esterified serum cholesterol is greater than the free cholesterol specific activity.[9] In man this was not the case; indeed the reverse was demonstrated, the free cholesterol initially having a higher specific activity than the esterified fraction. The explanation of this difference remains to be clarified. Whether this represents a fundamental species difference in metabolic pathways or whether the observed difference is a quantitative one of "defective processing" in the case of the rabbit remains to be seen.

Correct analysis of the blood cholesterol specific activity curves presented in figures 1 to 3 is extremely difficult, for the curves most assuredly reflect the integration of a large number of metabolic processes continuing at various rates. For the first 48 to 72 hours, during the initial rising portion of the curves, intestinal absorption and transport of the absorbed cholesterol to the systemic circulation via the lymph of the thoracic duct would appear to be paramount in determining the shape of the curve. It has been demonstrated previously that liver cholesterol and serum cholesterol are in rapid equilibrium[9, 10] and the initial steep descending portion of the curves occurring at two to five days probably represents a period during which serum cholesterol is exchanging with various tissue cholesterol pools, particularly liver. The terminal flattened portion of the curves would appear to approach the turnover rate of body cholesterol as a whole.

The observation that red blood cell cholesterol, following an initial lag period, reaches an equilibrium state with the free cholesterol of the serum in vivo confirms in man the previous observations of Hazerman and Gould.[10, 11] The presence of tritium-cholesterol in all of the various lipoprotein species after a period of 24 hours following the cholesterol meal in patient 1 is of interest. It has been shown in rats that absorbed cholesterol is transported via the lymph of the thoracic duct to the systemic circulation.[12, 13] Ultracentrifugal studies on such lymph would indicate that newly absorbed cholesterol is in both the esterified and free states and exists in or is associated with a lipoprotein structure with an S_f rate

greater than 100. The equilibrium state found after 24 hours in patient 1, with cholesterol from all of the lipoprotein species having the same specific activity, requires that the in vivo metabolism of serum lipoproteins involves a fairly rapid interchange of cholesterol moieties whether esterified or free. The mechanism for this remains to be elucidated. Preliminary in vitro studies of the interchange of cholesterol between various isolated lipoprotein species of different S_f rates indicate that free cholesterol exchanges rapidly but that esterified cholesterol does not.

At this stage in our knowledge of fecal steroid metabolism certain limitations on the interpretation of the total tritium content of the feces in patients 2 and 3 must be realized. On good and varied evidence[14–16] it has been held that the conversion of cholesterol to coprosterol goes via cholestenone and occurs within the intestinal lumen of the large bowel. Gallagher[4] has demonstrated that the in vitro conversion of deuterium cholesterol to cholestenone may result in the loss of 46 per cent of the deuterium label. Thus the possibility exists that during the formation of coprosterol from cholesterol some tritium label might exchange; however, at present the evidence would indicate that this does not occur. The in vivo formation of cholic acid[17] and pregnanediol[18] from cholesterol presumably via cholestenone does not result in loss of the label at C.[3–6] Of course if tritium exchange did occur with a substance that was absorbed, estimations of the amount of cholesterol absorbed by a measure of the amount of label disappearing from the feces would be in error. Experiments in which tritium-cholesterol and C^{14}-labeled cholesterol have been fed to rats do not show a greater disappearance of the tritium-label from the gut above that of the C^{14} label.[19]

At present it is permissible to say that the 87.4 per cent of the ingested tritium in patient 2 and 56.9 per cent in patient 3 found in the feces represents minimum values for the percentage of unabsorbed cholesterol. The 12.6 per cent and 42.1 per cent respectively which disappeared from the gut probably was absorbed as tritium-cholesterol. It is important here to point out that patient 2 received the tracer cholesterol in the crystalline form while patient 3 received hers dissolved in warm Wesson oil. An experiment to evaluate some of the factors important in man in determining the efficiency of cholesterol absorption, such as the physical state of the ingested cholesterol, is at present under way. The possibility, of course, exists that patients with hypercholesterolemia and xanthoma tuberosum absorb cholesterol more completely than patients with "normal" serum cholesterol values. This point of course requires more study.

Patient 4 requires a brief comment. The lipid metabolism of a dying, fasting man as might be expected appears to be grossly altered from that found in a normal, feeding person. Two other comatose patients with cerebrovascular accidents were studied simultaneously with patient 4. Each of these patients showed only trace amounts of the ingested cholesterol in the blood. Fecal collections were not possible here because of irregularity of stools and fecal incontinence. Presumably the very low serum cholesterol specific activities indicate very poor cholesterol absorption.

It was possible, however, in patient 4 to make a qualitative demonstration of exogenous cholesterol entering into the metabolism of the human atherosclerotic aorta. The amount of cholesterol isolated from the aorta (1.31 Gm.) and the specific activity found (0.03 μc. per gram) preclude the possibility that the activity found in the aorta could have been in blood or lymph cholesterol contained in the processed sample. To label 1.31 Gm. of cholesterol to a specific activity of 0.03 μc. per gram would require the inclusion of all the cholesterol from approximately 29 cc. of blood with a specific activity equal to 0.58 μc. per gram of cholesterol, the value present in serum cholesterol on day 29. The aortic sample processed weighed only 36.0 Gm.

If an approximated average serum cholesterol specific activity value of 0.6 μc. per gram is assumed for the period of the experiment, it can be estimated that an appreciable amount ($\sim$65 mg.) of the 1.31 Gm. of cholesterol isolated from the aortic sample arose from the serum as the result of the intermetabolism of

aortic cholesterol and serum cholesterol during the 43 day period.

Summary

Tritium-labeled cholesterol was used to investigate certain aspects of the metabolism of ingested cholesterol in four human subjects, all of whom presumably had atherosclerosis.

1. Cholesterol absorption is not efficient in man; however, approximately 12.6 per cent, 9.3 per cent and 19.2 per cent of the administered tritium-cholesterol could be demonstrated in the circulating blood two days after the tritium-cholesterol feeding in patients 1, 2 and 3 respectively.

2. Cholesterol absorption in man is slow and a peak serum cholesterol specific activity following a single labeled cholesterol feeding occurs in from 36 to 72 hours.

3. Serum free cholesterol has a higher specific activity than esterified cholesterol for 24 to 48 hours after a single tracer cholesterol meal. This is the reverse of that previously found in cholesterol-fed rabbits where the specific activity of the esterified cholesterol was the greater.

4. The specific activities of cholesterol isolated from the various lipoprotein fractions of the serum separated ultracentrifugally were identical 24 hours after the tritium-cholesterol feeding.

5. Free serum cholesterol and red blood cell cholesterol are in equilibrium in vivo.

6. Quantitative determinations of the tritium content of the feces for seven days following a tritium-cholesterol meal were made in two patients.

7. The qualitative demonstration of exogenous cholesterol entering into the metabolism of the human atherosclerotic aorta was made.

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Deposition and Disappearance of Digitoxin from the Tissues of the Rat, Rabbit, and Dog after Parenteral Injection

By Meyer Friedman, M.D., Shirley St. George, Ph.D., René Bine, Jr., M.D., Sanford O. Byers, Ph.D., and Catharine Bland, A.B.

Digitoxin administered to the rat, rabbit, or dog has no specific avidity for heart muscle. The quantity recovered from this organ at any time was no greater than from liver or kidney, while these organs continued to contain the glycoside for a much longer period of time.

THE DIGITALIS glycosides have proved themselves so efficacious in the treatment of various cardiac disorders that it is frequently forgotten that, nevertheless, there is little *exact* knowledge about either the pharmacologic or physiologic properties of these substances. For example, the exact quantitative aspects of the processes by which digitalis glycosides are (1) absorbed from the gastrointestinal system, (2) carried in the blood stream, (3) enter various tissues and organs, and (4) are disposed of by these same tissues, are in the main unknown. Likewise, the means by which these drugs effect their benign changes in a deranged cardiovascular system still remain to be understood.

Undoubtedly one of the chief difficulties attendant on an investigation of the fate of digitalis glycosides in the body has been the absence of a tool sufficiently sensitive to measure their concentration in various tissues. Thus, although some aproximations have been made concerning the fate of these substances in the mammalian body, the data allowing them have been obtained too often from experiments in which huge amounts of the drug have been given. Or else data have been gathered from experiments in which *isolated* preparations have been perfused with moderately dilute solutions of glycoside or digitalis. It can be understood that neither type of experiment is ideal, either from a physiologic or pharmacologic viewpoint.

Recently, however, by the use of the embryonic duck heart preparation we have been able to follow the initial deposition and later, the rate of disappearance of digitoxin from the tissues of various *intact* animals after parenteral injection of the drug. The present article gives the results of this study.

Methods

A. *Rat.* Samples of the heart, liver, kidney, lung, muscle, spleen, and brain were removed from groups of rats, immediately, 1, 3, 6, 10, 12, and 16 hours after intravenous injection of digitoxin (1 μg. per gram of body weight). Samples of the brain also were removed from groups of rats 24 and 48 hours after injection of digitoxin. One gram quantities of each sample then were analyzed for their digitoxin content according to previously described methods.[1] In this manner, the fate of digitoxin in various tissues of the intact, normal rat could be followed.

B. *Rabbit.* Samples of heart, liver, kidney, and lung of rabbits were obtained immediately, and one hour after the injection of digitoxin (0.5 μg. per gram of body weight). They were analyzed for digitoxin exactly as the rat tissues had been. It was found in preliminary studies that known amounts of added digitoxin could be removed completely from the tissues studied. A second series of rabbits was injected with 0.2 μg. of digitoxin per gram of body weight and the tissues were obtained and analyzed immediately, one half, one, and three hours after injection.

C. *Dog.* Samples of the heart, liver, kidney, and lung were obtained immediately, 1, 2, 4, 8, 16, 24, and 48 hours after the injection of digitoxin (0.2 μg. per gram of body weight). Analyses of these tissues for digitoxin content were similar to those done on the rat and rabbit tissues.

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TABLE 1.—*Deposition and Disappearance of Digitoxin from Tissues of the Rat, Rabbit, and Dog*

Time after Injection (Hrs.)	No. Exps.	Digitoxin (μg.) per Gram						
		Heart	Liver	Kidney	Lung	Muscle	Spleen	Brain
Rat								
0	7	2.0 (1.0–2.5)†	6.0 (5.0–7.5)	2.7 (1.0–5.0)	2.7 (1.0–5.0)	0.25 (0.25–0.25)	0.45 (0.25–0.8)	N.D.*
1	6	1.85 (0.5–2.5)	4.6 (2.5–5.0)	2.0 (1.0–2.5)	2.0 (1.0–2.5)	0.30 (0.25–0.50)	0.25 (0.25–0.30)	N.D.
3	6	0.40 (0.2–0.5)	2.1 (1.0–2.5)	0.6 (0.5–1.0)	0.4 (0.2–0.50)	0.30 (0.25–0.50)	0.15 (0.1–0.20)	0.10 (0.05–0.20)
6	5	0.30 (0.2–0.5)	2.5 (1.00–5.0)	0.6 (0.25–1.25)	0.5 (0.4–0.6)	0.20 (0.1–0.4)	0.20 (0.1–0.4)	0.20 (0.15–0.25)
10	5	0.05 (0.05–0.10)	1.2 (1.0–2.0)	0.25 (0.1–0.4)	0.05 (0.05–0.10)	0.05 (0.05–0.05)	0.05 (0.05–0.05)	0.20 (0.15–0.25)
12	5	N.D.	0.05 (0.05–0.05)	N.D.	N.D.	N.D.	N.D.	—
16	5	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.20 (0.10–0.30)
24	7	—	—	—	—	—	—	0.05 (0.05–0.05)
48	4	—	—	—	—	—	—	N.D.
Rabbit								
0	2	3.4 (2.5–4.2)	4.2 (3.5–5.0)	3.5 (2.0–5.0)	3.0 (2.5–3.5)	—	—	N.D.
1	6	0.3 (0.2–0.45)	0.6 (0.4–1.0)	0.55 (0.10–1.0)	0.35 (0.1–0.80)	—	—	N.D.
Dog								
0	2	0.20 (0.20–0.20)	0.30 (0.2–0.40)	0.40 (0.3–0.5)	0.25 (0.2–0.30)	—	—	—
1	3	0.30 (0.2–0.45)	0.20 (0.15–0.2)	1.50 (1.0–2.0)	0.10 (0.1–0.1)	—	—	—
2	2	0.20 (0.2–0.2)	N.D.	1.0 (1.0–1.0)	N.D.	—	—	—
4	2	N.D.	N.D.	1.25 (1.0–1.5)	N.D.	—	—	—
8	3	N.D.	—	1.30 (0.5–2.0)	—	—	—	—
16	2	N.D.	—	0.20 (0.2–0.2)	—	—	—	—
24	2	—	—	0.35 (0.2–0.5)	—	—	—	—
48	2	—	—	N.D.	—	—	—	—

* Nondetectable
† Range of Values

RESULTS

A. *The Deposition and Disappearance of Digitoxin from the Tissue of Various Animals*

1. *The Rat.* As table 1 illustrates, the liver of the rat contained digitoxin at a concentration far exceeding that of the heart or any other organ. This predilection of the drug for the liver, moreover, continued for a considerable period of time. Certainly the glycoside displayed no especial affinity for the heart. This last fact also was demonstrated by the observa-

tion that both the kidney and lung contained either as much or more digitoxin than the heart. Skeletal muscle and spleen on the other hand, contained less digotoxin than the heart.

Unlike the other tissues studied, brain apparently received little digitoxin until about three hours after its injection, but then (see table 1) it continued to exhibit the drug long after it could not be detected in any other organ. This last observation suggests that the rate of transfer of the glycoside both into or out of brain tissue is exceedingly sluggish. In other words, the brain is the last tissue to accept digitoxin and the last to give it up.

Ten hours after the injection of digitoxin, although all tissues of the rat still contained the drug, its concentration in any tissue was very slight except in the liver which still contained 1.2 μg. per gram. Twelve hours after injection, even the liver contained very little (0.05 μg. per gram) and none was detectable in the remaining viscera. Digitoxin at 16 hours, could be detected only in the brain.

2. *The Rabbit.* Similar to the rat heart, the rabbit heart also did not appear to concentrate digitoxin in any extraordinary fashion. (See table 1.) Thus, the heart was not found to contain significantly larger amounts of digitoxin immediately after injection than the kidney or the lung. Actually the liver, as had been noted in the study of rat tissues, contained more digitoxin than the heart. Moreover, one hour after injection, the kidney as well as the liver was found usually to contain more digitoxin than the heart. No digitoxin was detectable in the brain.

The fate of digitoxin in the tissues of the rabbit could be determined one hour after the injection of 0.5 μg. per gram but not after this period of time because the animals died shortly after an hour as a result of the effects of the drug. When a series of 13 rabbits was given only 0.2 μg. of digitoxin per gram of body weight, the heart again was found to contain approximately the same amount of digitoxin (0.5 μg. per gram) immediately after injection as was found in the lung and kidney. Moreover, 30 minutes after injection, the heart contained only 0.1 μg. of digitoxin per gram compared to a concentration of 0.3 μg. per gram in the liver and kidney. At the end of one hour, only the kidney was found to contain a small amount of digitoxin (0.1 μg. per gram). At the end of three hours, the kidney also failed to exhibit any detectable digitoxin.

3. *The Dog.* Digitoxin after its intravenous injection into the dog was found to have no predilection for cardiac tissue. (See table 1.) Immediately after the injection of 0.2 μg. of digitoxin per gram of body weight, most of the organs contained about the same amount of drug (0.2 μg. to 0.4 μg. per gram). The heart, however, appeared to retain its digitoxin longer. Thus, one hour after injection, more digitoxin was found in the heart (0.3 μg.) than in the liver (0.2 μg.), or lung (0.10 μg.). (See table 1.) However, even at this time there was very much less in the heart than in the kidney (1.5 μg.). Two hours after the injection only the heart and the kidney exhibited digitoxin. From this period on, up to 24 hours, digitoxin was found only in the kidney and in diminishing amounts in this organ.

Discussion

The present study indicates that digitoxin appeared capable of entering each tissue of the rat and other species assayed. Its tardiness in entering and leaving the brain of the rat and its absence in the rabbit brain (one hour after injection) might have been expected for apparently the blood brain barrier is not too easily trespassed in either direction by steroids.

If digotoxin, however, enters most tissues there is little evidence from the results of our analyses that it has extraordinary avidity for cardiac tissue, as has been reported.[2] Thus, in the rat, rabbit, and dog, the amount of digitoxin deposited in the heart immediately after its injection appears to be about the same as that deposited in the lung or kidney. Moreover, the heart of the rat and rabbit did not appear to retain excess digitoxin any longer than other tissues. Only the dog's heart appears to retain digitoxin slightly longer than such tissues as the lung and liver.

On the other hand, there was considerable evidence in the present studies that digotoxin is found in greatest concentration in those organs which excrete the drug. Thus, the liver

of the rat (which has been found capable of excreting digitoxin[3]) was found to contain, 10 hours after injection of digitoxin, over 20 times as much of the drug as the heart. On the other hand, the dog excretes significant amounts of digitoxin in his urine,[4] and his kidney accordingly was found to contain five times as much digitoxin as his heart, two hours after parenteral administration.

The present studies offer little information concerning the possible destruction of digitoxin in various tissues of the animal body. In other words, the disappearance of the drug from various tissues could be due to its escape back into the blood and its excretion by the liver, intestine, or kidney. Recently, however, Sjoerdsma and Fischer[5] concluded that their perfused heart preparation broke down 30 to 40 per cent of the digitoxin it absorbed, all in a period of 5 to 20 minutes. It should be mentioned, however, that their basis for this assumption was their inability to extract the entire amount of digitoxin calculated to have been absorbed by their perfused heart. It has been our experience, however, that *chloroform extraction* of any tissue homogenate for its content of digitoxin may be incomplete if the amount of the drug in the homogenate is minute.

If various tissues do have the power to destroy digitoxin, it is probably a process intimately attuned to the amount of the drug presented to the tissue. Thus, when small amounts of the drug are presented to various organs as is probably the case in man, the process of destruction must be exceedingly slow or limited. Otherwise, the prolonged persistence of the drug in the body and its gradual renal excretion over a period of several weeks[6] becomes inexplicable. On the other hand, if moderately *large* amounts are administered as in the present experiment, considerable destruction in certain tissues might be expected to take place. This last possibility, however, remains to be demonstrated.

Summary

1. The amount of deposition and consequent rate of disappearance of digitoxin from various tissues of the rat, rabbit, and dog after parenteral administration of the drug were studied.

2. No special predilection was shown by digitoxin for deposition in the cardiac tissue of any animal studied although the heart of the dog retained digitoxin longer than did some of its other organs. Even in this animal, however, the kidney contained detectable amounts of digitoxin far longer than the heart.

3. Concentration of digitoxin appeared to occur in the body organ(s) chiefly involved in its excretion. Thus, it was found in highest concentration in the liver of the rat and in the kidney of the dog.

4. Digitoxin disappeared slowly from the tissues of the rat and dog but rather rapidly from the tissues of rabbit.

5. The possible fate of digitoxin in the animal and human body was discussed in the light of the above observations.

The authors wish to express thanks to Pamela Angwin and Tadashi Ishida for technical assistance.

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Correlation of Serum Potassium Concentrations with the Blood Pressure in Rats Fed a Potassium-Deficient Ration

By SHIRLEY M. ST. GEORGE, PH.D., S. CHARLES FREED, M.D., AND RAY H. ROSENMAN, M.D.

Rats which develop low blood pressures as a result of low potassium diet are shown to have lowered serum potassium levels. When the blood pressure is restored to normal by injection and 24 hour feeding of potassium, serum potassium levels also return to normal.

WHEN RATS are deprived of potassium by dietary restriction, there is a significant lowering of the blood pressure.[1, 2] This occurs in animals made hypertensive[3] as well as in normal rats. Furthermore, there is a prompt restoration of the blood pressure to normotensive levels when potassium is administered to such animals.[4] It therefore was considered important to determine whether the hypotensive effect of potassium-deficiency and the return to normal blood pressure levels following potassium administration could be correlated with the blood serum potassium concentrations.

METHODS

Two groups of 6 to 8 weeks old, male, Long-Evans rats were subjected to the following procedures. Group I (31 rats) was fed a potassium-deficient diet.[3] Group II (11 rats) was fed the identical diet to which was added 0.5 per cent potassium chloride. Systolic blood pressures of all rats were determined after 12 weeks by the microphonic manometer method.[5]

At the end of this period 18 rats of group I and all those of group II were sacrificed and blood was obtained by aortic puncture and analyzed for serum potassium concentrations with a Barclay flame photometer. The remaining 13 rats of group I received 10 ml. of isotonic potassium chloride solution (155 mEq. per liter) by subcutaneous administration. They were then permitted to drink 1 per cent potassium chloride solution ad lib. for the next 24 hours, during which time all food was withheld. At the end of this 24-hour interval their blood pressures again were taken and serum potassium determinations were made.

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This work was done during the tenure by R.H.R. of a Research Fellowship of the American Heart Association.

RESULTS

The serum potassium concentration of the control rats (group II) was found to average 5.59 mEq. per liter (range: 5.05 to 6.6; S.E. Mean: ±0.15), values in accord with the results of other investigators.[6] This was associated with an average blood pressure of 109 mm. Hg (range: 96 to 130; S.E. Mean: ±3.0). The 18 rats in group I, which were fed the potassium-deficient diet, had an average serum potassium concentration of 2.9 mEq. per liter (range: 2.48 to 3.25; S.E. Mean: ±0.067), and an average blood pressure level of 86 mm. Hg (range: 72–100; S.E. Mean: ±5.0). The remaining 11 rats in group I also received the potassium-deficient diet. Twenty-four hours after administration of potassium parenterally and orally, the average serum potassium concentration was 6.4 mEq. per liter (range: 4.8 to 7.8; S.E. Mean: ±0.3). The average blood pressure increased from a level of 81 mm. Hg (range: 62 to 94; S.E. Mean: ±2.65), prior to administration of potassium, to 101 mm. Hg (range: 68 to 124; S.E. Mean: ±4.8), when taken 24 hours after the administration of potassium.

DISCUSSION

From the above results it was apparent that the rats with hypotension following dietary potassium-deprivation have markedly

reduced serum potassium concentrations. When such rats received sufficient potassium, the serum concentration of this salt increased to normal values within 24 hours. At the same time the blood pressures returned to normal levels. Under the conditions of these experiments, there appeared to be a significant correlation between serum concentration of potassium and the blood pressure level.

Summary

The hypotensive response occurring in rats fed a potassium-deficient diet was found to be associated with a marked hypopotassemia. The rapid return of the blood pressure of such rats toward normotensive levels, following the administration of potassium alone, was found to be associated with a return to normal of the serum potassium concentration.

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Pressor Effects of Epinephrine, Norepinephrine and Desoxycorticosterone Acetate (DCA) Weakened by Sodium Withdrawal

By W. Raab, M.D., R. J. Humphreys, M.D., N. Makous, M.D., R. DeGrandpré, M.D., Ph.D., and W. Gigee, R.N., A.B.

Recent findings suggest an important role of the sodium ion, intracellularly deposited by the adrenal mineralocorticoids, as the physicochemical mediator between the pressor actions of the mineralocorticoids and of the adrenosympathogenic neurohormones. The following observations show that the pressor effectiveness of both the pressor neurohormones and desoxycorticosterone acetate depends on the availability of sodium. This supports the theory that vascular pressor responsiveness and tonus is determined jointly by the sodium-depositing corticoids as sensitizers and the adrenosympathogenic neurohormones as the physiologic stimulators of the vascular contractile elements.

An important role of the local action of electrolytes in the maintenance of vascular tone was postulated by Loeb[1] and Swingle[2] 10 years ago. In the meantime, it was found that the slow pressor effect of desoxycorticosterone acetate (DCA) is enhanced by sodium ingestion[3–8] and weakened or abolished by sodium withdrawal.[3,9–12] These observations suggested that the sodium ion is fundamentally involved in the pressor action of desoxycorticosterone and probably also of the natural mineralocorticoids.

Furthermore, it has been shown in previous publications[13, 14] and confirmed by others[3, 15] that the pressor effects of injected or infused epinephrine and norepinephrine in man are potentiated by pretreatment with desoxycorticosterone. On the other hand, in adrenalectomized animals[16, 17] and in hypoadrenocortical human subjects,[18, 19] the pressure ceilings after epinephrine injection proved to be lowered.

It appeared possible, therefore: (a) that adrenal mineralocorticoid activity might be an important factor in determining the degree of cardiovascular pressor responsiveness to the adrenosympathogenic catecholamines (epinephrine, norepinephrine) by virtue of its influence on electrolyte balance, and (b) that the pressor effect of desoxycorticosterone itself might be due to an increase of vascular contractile reactivity to intrinsic catecholamine (norepinephrine) action as a result of intracellular sodium deposition.

The following experiments were carried out in order to study the influence of dietary salt withdrawal (a) upon the pressor responses to infused epinephrine and norepinephrine, and (b) upon the epinephrine- and norepinephrine-potentiating action of desoxycorticosterone.

Methods

In four patients (three moderately, one markedly hypertensive), all of whom had been hospitalized for weeks or months prior to the beginning of the experiments,* the average pressor effects of intravenously infused epinephrine and norepinephrine (0.1 or 0.2 or 0.3 μg per kilogram per minute for five minutes each) were recorded with the same technic as published elsewhere.[14] Thereupon, the patients were placed on a sodium-poor, rice-fruit diet, containing 180 mg. of sodium per day. During certain periods of this regime, desoxycorticosterone was administered intramuscularly in daily doses of

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* Three of the patients were located at the Vermont State Hospital in Waterbury. We want to express our thanks to the Superintendent, Dr. Rupert Chittick, for the permission to work there, and to the hospital staff for efficient assistance.

10 mg.† (corresponding to the dosage and duration of administration which had regularly intensified the pressor catecholamine effect in another series of experiments[14]). The experimental periods were concluded with the resumption of a normal diet with or without desoxycorticosterone. During all phases of these procedures, repetitions of the epinephrine and norepinephrine infusions were carried out with the same dosages as at the beginning.

Sodium and potassium in serum and urine were determined with a flame photometer. In the cases of two patients who were incontinent and two others who were mentally disturbed it was not always possible to collect complete 24-hour specimens. Consequently, the urine electrolytes were expressed in these cases in milliequivalents per liter and the readings represent only an approximate, indirect measure of the total daily excretion. These tests served mainly the purpose of checking the reliability of the patient's dietary discipline. In one case, the sodium assay in the urine revealed the temporary surreptitious ingestion of extra salt.

Results

The systolic and diastolic blood pressure data, represented in figures 1 through 4, indicate: (a) resting levels in recumbent position after preparatory rest periods (no sedatives); (b) pressor responses to infused epinephrine and norepinephrine, that is, the absolute pressure deviations from the respective resting levels; (c) pressure ceilings, that is, the pressure levels, reached under the influence of epinephrine or norepinephrine infusion. Each value for (b) and (c), appearing in figures 1 through 4, represents the average of five readings, taken during a five-minute infusion period. (For explanation of graphs, see legend to fig. 1.)

During sodium withdrawal, the systolic resting pressure level was decreased in all four cases. Administration of desoxycorticosterone during the period of sodium deprivation failed to raise the blood pressure, except in one instance (fig. 3). With resumption of a normal diet, the systolic pressure levels (without or with desoxycorticosterone) tended to return toward their original height with individually different speeds. The diastolic pressure levels behaved generally in a similar fashion but within narrower ranges.

† We are indebted to Ciba Laboratories, Inc., for a generous supply of Percorten (desoxycorticosterone acetate).

The absolute systolic and, less regularly, the diastolic pressor responses to infused epinephrine and norepinephrine were weakened or occasionally abolished during salt withdrawal.

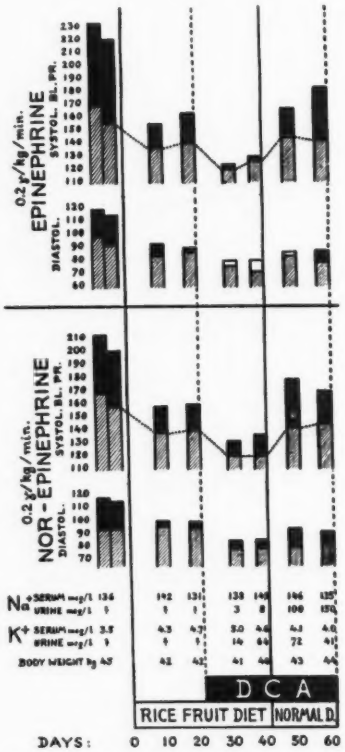

FIG. 1. Case 1. Resting blood pressure is shown by the upper limit of each shaded area where a black area is superimposed, and by the top line where a white area is superimposed. Absolute increments of the blood pressure during epinephrine and norepinephrine infusions are represented by black areas, absolute decreases of the blood pressure by white areas. Each graphically symbolized blood pressure response to infused epinephrine or norepinephrine represents the average of five readings made during a five-minute infusion period.

The systolic and, less markedly, the diastolic pressor ceilings were lowered throughout.

Administration of desoxycorticosterone during salt withdrawal failed to increase the pressor effects of epinephrine and norepinephrine. Resumption of a normal diet, without or with desoxycorticosterone, was followed by a grad-

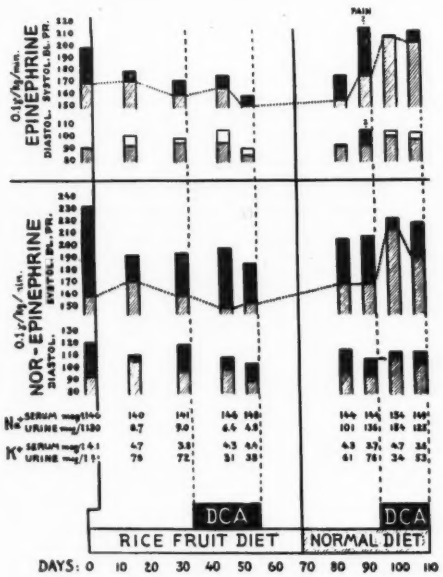

FIG. 2. Case 2. See legend for figure 1.

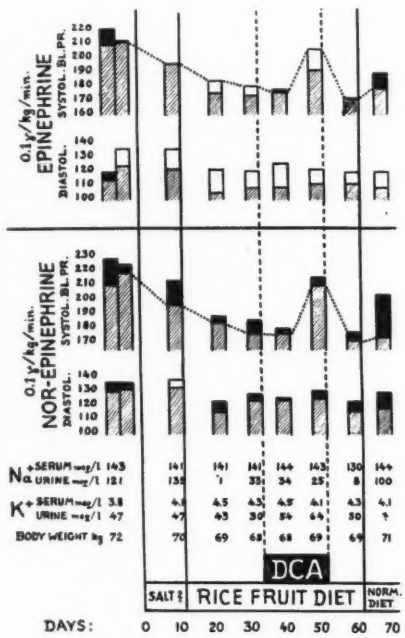

FIG. 3. Case 3. See legend for figure 1.

ual return of the pre–rice diet pressor responses to epinephrine and norepinephrine.

The serum sodium concentrations varied irregularly and without any recognizable relationship to blood pressure levels and pressor responses. The serum potassium level was not significantly affected by the salt-poor diet. Desoxycorticosterone administered during salt withdrawal, did not depress the serum potassium concentration.

In one case, not reported in this series, the intake of a diet containing a larger amount (400 mg.) of sodium per day caused a moderate decline of the resting blood pressure, but only an insignificant lowering of the catecholamine-induced pressure ceilings. Desoxycorticosterone restored both to the pre-experimental levels.

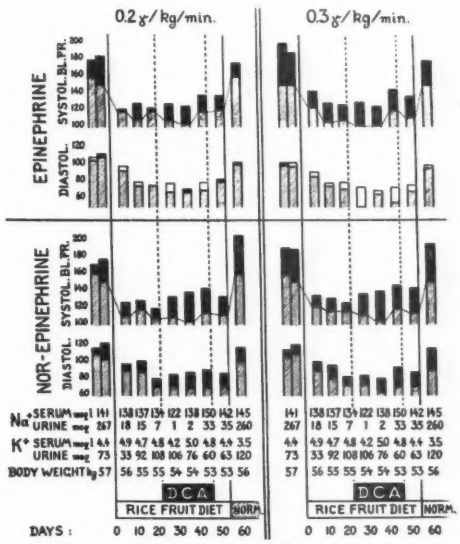

FIG. 4. Case 4. See legend for figure 1.

DISCUSSION

The salient points among the findings obtained are the following: (a) the absolute pressor effects (predominantly systolic) of epinephrine and norepinephrine, and even more so their ceiling effects, were significantly diminished or abolished by intake of an almost sodium-free rice-fruit diet; (b) during sodium withdrawal, desoxycorticosterone failed to intensify the pressor effects of epinephrine and norepinephrine, in contrast to its normally potentiating action upon these effects.

These observations suggest that the presence of a certain amount of sodium in the body is

necessary to maintain full cardiovascular pressor responsiveness to both adrenosympathogenic neurohormonal stimuli and desoxycorticosterone (adrenal mineralocorticoids?). Desoxycorticosterone intensifies the pressor effectiveness of the adrenosympathogenic catecholamines during normal salt intake,[3,13–15] probably by retaining sodium in the body, and particularly by its specific ability to augment the intracellular sodium concentration.[20–26]

The results obtained during intake of the rice-fruit diet are ascribed to the lack of sodium and not to other peculiarities of this diet, since its blood pressure-lowering action could be duplicated by various mixed diet forms, provided that their sodium content was low.[9,27–31]

The fact that in one case a somewhat higher sodium intake (400 mg. per day) failed to produce a striking effect on the pressor reactions seems to indicate that sodium restriction must be extreme to alter the vascular reactivity significantly.

The slowness of the return to pre–rice diet reactions after resumption of a normal salt intake in three out of the four cases may possibly be explained as the result of a temporary adrenal cortical functional insufficiency, caused by the preceding periods of desoxycorticosterone administration.

Neither the phenomenon of a potentiation of catecholamine pressor effectiveness by desoxycorticosterone nor the opposite weakening effect of salt withdrawal would be of any particular interest if these findings did not open a new outlook on the fundamentals of integrated nervous and hormonal blood pressure regulation. It appears conceivable that the interplay between the intrinsic sympathogenic pressor catecholamines (mainly norepinephrine) and adrenal mineralocorticoids maintains, elevates, or depresses the blood pressure level whereby sodium seems to act as the physicochemical mediator. It has recently been shown that the contractile power of muscular elements depends on their electric membrane potentials and that the latter in turn are determined by the gradient between intra- and extracellular electrolyte concentrations.[32, 33] The significance of desoxycorticosterone for muscular activity by its apparent action on cell membranes and intracellular electrolyte distribution was demonstrated specifically concerning the heart muscle.[38] Furthermore, epinephrine and norepinephrine have been recognized as depolarizing agents.[34–36] These important findings are likely to facilitate the understanding of hypertensive and hypotensive mechanisms on a physicochemical basis. A tentative interpretation of the integrated role of catecholamines, mineralocorticoids and sodium in the origin of hypertension and in the mechanism of action of successful therapeutic procedures, such as sympathectomy, salt-poor diet and adrenalectomy, will be presented elsewhere.[37]

Summary

During intake of a practically sodium-free diet, the following effects were observed in four hypertensive patients: (a) the resting blood pressure declined; (b) the pressor effectiveness of infused epinephrine and norepinephrine was significantly weakened or abolished; (c) desoxycorticosterone failed to intensify the pressor effects of epinephrine and norepinephrine in contrast to its normally potentiating action.

Brief reference is made to the conceivably integrated role of adrenosympathogenic catecholamines, mineralocorticoids and the sodium ion in the neurosecretory and hormonal system of blood pressure regulation.

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The Measurement of the Q-T Interval of the Electrocardiogram

By EUGENE LEPESCHKIN, M.D., AND BORYS SURAWICZ, M.D.

The sources of error in determination of the beginning of QRS and the end of T during measurement of the Q-T duration are analyzed. An important error is confusion of an elevated U wave with the T wave, resulting in the diagnosis of a prolonged Q-T. In such cases, some of the precordial leads usually show a notch or kink between T and U which indicates approximately the end of T. If these criteria are used, the true corrected Q-T duration in hypopotassemia without hypocalcemia is not prolonged, but normal or shortened, corresponding to an earlier appearance of the second heart sound.

THE DURATION of the Q-T interval of the electrocardiogram in its relation to the heart rate (relative or corrected Q-T duration) has been receiving increasing attention during the last decade. It has been found of especially great practical importance in the diagnosis of myocarditis[13, 24, 38, 41] and of certain diseases accompanied by electrolyte imbalance (literature quoted in reference 24). It is also of importance in the determination and evaluation of the ventricular gradient.[24] The sources of error which may appear in the determination of the corrected Q-T duration are threefold. First, there are difficulties in the exact determination of the points which are to be used for the measurement of the Q-T interval in a given complex. Second, there are difficulties in averaging the Q-T duration of different complexes, which shows physiologic fluctuation even at constant heart rates, but especially when the heart rate varies, as for instance in respiratory arrhythmia and auricular fibrillation. A third group of difficulties arises when the actually measured Q-T duration is corrected for the heart rate and, in some cases, for a prolonged QRS duration. The two last mentioned groups of difficulties were adequately discussed and partly clarified in previous publications.[2, 3, 10, 16, 25, 35, 36, 38, 42, 47] The first source of error, that of actual measurement, was recognized by some authors,[16, 22, 23, 25, 27, 32, 37, 42] but no systematic treatment of this subject was attempted up to the present time. In many cases the difficulties in the definition of the points to be used for measurement are so great that different cardiologists would probably assign widely diverging values to the Q-T interval of the same tracing. The purpose of the present paper is to point out some of these difficulties and to attempt to develop a set of exact rules and methods which could be used in future studies.

There can be no divergence of opinion that the Q-T duration should be measured from the beginning of the QRS complex to the end of the T wave. There are two main sources of error in measuring the Q-T duration. The Q-T duration can appear either shorter or longer than in reality. It can appear shorter if the first or last potentials produced during ventricular systole are directed perpendicular to the lead or, in other words, the initial portion of the QRS group or the terminal portion of the T wave may be isoelectric. It can, furthermore, appear shorter if parts of the T wave have an unusual configuration and are confused with other waves of the electrocardiogram, such as the P or U waves. The Q-T duration can appear longer than it is if other waves (usually the U wave, sometimes the P wave) are mistaken for the T wave proper or for the terminal part of a notched T wave. We shall consider each of

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the above sources of error systematically in the following paragraphs.

1. Isoelectric Beginning of QRS

It is a well known fact that QRS begins earlier in the chest leads V_{1-3} than in leads V_{4-6} or in the limb leads.[24, 39a] The most exact values of Q-T can therefore be obtained in leads V_{2-3}, if the T wave can be adequately measured in these leads (see later). If it is possible to register two or more leads synchronously, the point corresponding to the earliest beginning of QRS in any of these leads must be taken as the beginning of Q-T. If no synchronous registration is possible, the three standard or unipolar limb leads, registered at standard sensitivity, can still be synchronized by moving them horizontally until lead II = I + III or lead $aV_R + aV_L + aV_F = 0$.[24] In most cases the error due to asynchronous beginning of QRS in different leads is small and does not exceed 0.02 second.[32]

2. Isoelectric End of the T Wave

The end of the T wave, like the beginning of QRS, may have an isoelectric course in one or more leads, but because of the long duration of T the differences are much greater than in the case of QRS and may reach 0.04 second (fig. 1). In leads where the T wave is very low, its terminal portion may show such low voltage as to be practically indistinguishable from the slight spontaneous fluctuations of the base line or the U wave. An isoelectric terminal portion of T also often precedes a terminal inversion of T.[24] It is therefore advisable to measure the Q-T duration in leads showing the highest voltage of T. These are usually the leads V_{2-4}. If it is possible to register synchronous leads or to synchronize the limb leads, it is always the latest point on the T wave in any lead which must be used for measuring Q-T, provided the T wave can be correctly identified.

3. Notched T Wave Mistaken for U Wave

The T wave usually has a smooth, curved form, but in a small number of cases, especially in leads from the transition zones between a positive and a negative T wave, it may show a notch near its summit. In this case the notch can be mistaken for the end of the T wave while the section of T beyond the notch is considered as a U wave. This mistake is especially easy if the notch approaches or reaches the base line. However, other leads, taken synchronously with the doubtful leads or synchronized with them subsequently, usually show T waves of the typical form, whose summits coincide with the notch. As an example, the notched

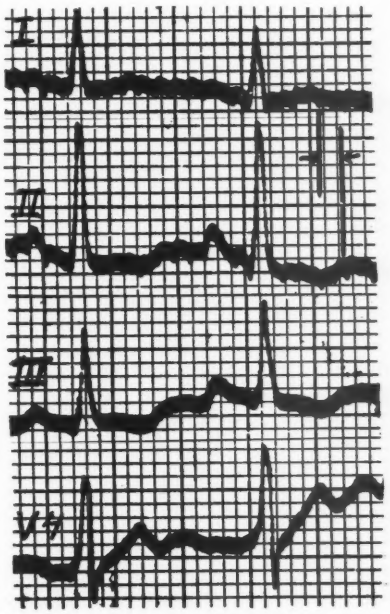

Fig. 1. Leads I–III and V_4, registered synchronously in an apparently normal person immediately after two minutes of exercise in the recumbent position. The Q-T duration in lead I is at least 0.04 second shorter than in leads II–III. The first complex of lead V_4 shows a definite kink between the terminal negative phase of a diphasic T wave and the positive U wave, while in the second complex the transition is more gradual.

T wave in lead V_3 of figure 2*c,d* which appeared as a transition between a normal and a terminally inverted T wave during exercise is synchronous with a smooth T wave in lead V_5.

The situation is more difficult if all the available leads show notched T waves; this occurs in pathologic cases, in some normal dogs[24] and usually in children.[24] If a distinct U wave is present in addition to the notched T wave, the differentiation is comparatively easy, as in

most of the published cases.[18, 49] (See also figure 61*H–J* of reference 22.) If the U wave is so low as to be indistinguishable, the following means of differentiation can be used: The terminal portion of T following the notch is usually of short duration (less than 0.15 second), while a U wave is longer; the slope of the

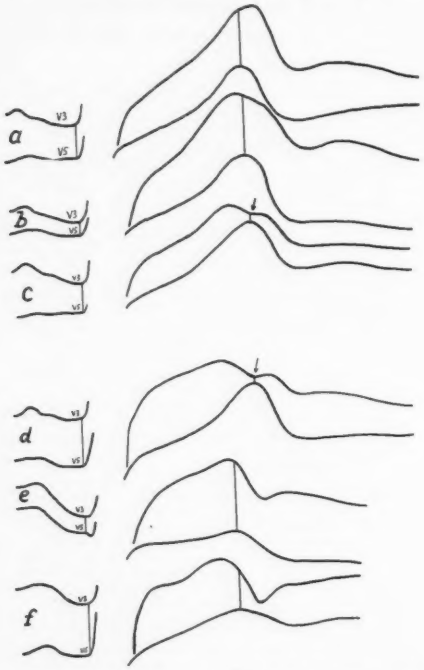

FIG. 2. Enlarged tracings of leads V_3 and V_5, registered synchronously in a patient with emphysema. The QRS complexes are not reproduced. The vertical lines in each pair of leads indicate the beginning of QRS and the apex of T in lead V_5. *a* and *b:* at rest; *c* and *d:* five minutes after exercise; *e* and *f:* one minute after exercise. The complexes in lead V_3 show a progressive transition from a monophasic positive T wave to a flat-topped T wave, a notched T wave (indicated by arrows) and a diphasic T wave with terminal negativity.

T wave exceeds 1 microvolt per millisecond while that of the U wave usually does not. According to tentative measurements, the distance between the two summits of a true notched T wave is shorter than that between the summit of T and that of U; the former usually does not exceed 40 per cent of the distance between the second summit and the beginning of QRS, while the latter usually exceeds 40 per cent of the distance between the summit of the U wave and the beginning of QRS. The notch in the T wave usually appears at least 0.04 second earlier than the second heart sound while the notch between T and U is usually situated within 0.04 second of this sound; this is discussed at greater length in the next section.

4. U Wave Mistaken for T Wave

If the U wave is separated from the T wave by a distinct isoelectric interval the two waves can be easily differentiated. However, in many of these cases the isoelectric interval is due to an isoelectric terminal portion of T (section 2), and the true end of T can be determined only by comparison with other leads. If the U wave follows the T wave immediately, without an isoelectric interval, it can be confused with the terminal portion of a notched or diphasic T wave. The 16 possible combinations of a positive, diphasic or negative T wave with a positive, diphasic or negative U wave are illustrated in figure 3 (solid parts of the figures).

In 8 of the 16 combinations in which the direction of the terminal limb of the T wave is opposite to that of the initial limb of the U wave, these two parts are separated by a distinct notch. In the other eight combinations where this direction is the same, the T and the U waves are separated by a kink, that is, by an abrupt change in the slope of the curve. This is due to the fact that the return of the T wave to the base line almost always is of a steeper slope than that contained in any part of the U wave. According to tentative measurements, the slope of the U wave usually does not exceed 1 μV per millisecond while the terminal portion of the T wave usually exceeds this slope. However, in cases where the T wave is depressed and the U wave elevated, the slope of the latter may approach the former. In this case the T wave and the U wave show an apparent merging and the end of the T wave can be determined only indirectly, as described in the following paragraphs, where each of the 16 patterns will be discussed in detail.

The combinations Ia and Ib (fig. 3) occur more often than any other. As long as the positive T and

U waves retain their characteristic shape, the differentiation of these two waves is easy; however, in the presence of a depressed T wave and an elevated U wave, the latter can be mistaken for the second summit of a bifid T wave. The differentiation of such cases has been discussed in section 3. In all cases of this pattern the end of the T wave is determined by the nadir of the notch between T and U.

The combinations Ic and Id, with a positive T wave and a negative initial portion of the U wave, appears sometimes after exercise or in pathologic cases.[20, 24, 31] The inverted U wave in pattern Id can be mistakenly held for the terminal negative part of a diphasic T wave (figure 2 and lead V_4 of figure 1), but the presence of a kink between the descending limbs of the T and U wave clearly designates the end of the T wave in most cases.

The patterns IIa and IIb, with a diphasic T wave showing terminal negativity and a positive initial portion of the U wave, present no great difficulties of differentiation if there is a definite kink between the ascending limbs of the T and U waves (for example, figure 2*f* and the first complex of lead V_4 in figure 1). In these cases the kink represents the end of the T wave. However, in some cases, such as the second complex of lead V_4 in figure 1, the kink is so indistinct that it cannot be located readily. In such cases an approach to the determination of the end of T can be made by considering the end of T as a point halfway between the summits of the T and U wave. A further means of differentiation can be found in the location of the II heart sound, as will be described more fully in section 5.

The patterns IIc and IId with a diphasic (plus-minus) T wave and a negative initial portion of U are rare. In these patterns the end of the T wave can be easily located at the apex of the notch between T and U (for example, tracing of 9.3.46. in figure 6 of reference 1).

The patterns IIIa and IIIb with a diphasic (minus-plus) T wave and a positive initial section of U usually present little difficulty in the determination of the end of the T wave, which coincides with the notch between T and U (for example, table 5 C of reference 15).

The patterns IIIc and IIId with a diphasic (minus-plus) T wave and a negative initial section of U present the same difficulties in the determination of the end of T as the patterns IIa and IIb. In these cases a definite kink is usually present between the descending limbs of the T and U waves (for example, lead V_5 of figure 4*a*). In cases where this kink cannot be readily identified, a point halfway between the apex of the positive portion of T and the nadir of the negative portion of U can be used as an approximation.

The patterns IVa and IVb with negative T wave and positive initial section of U almost always show

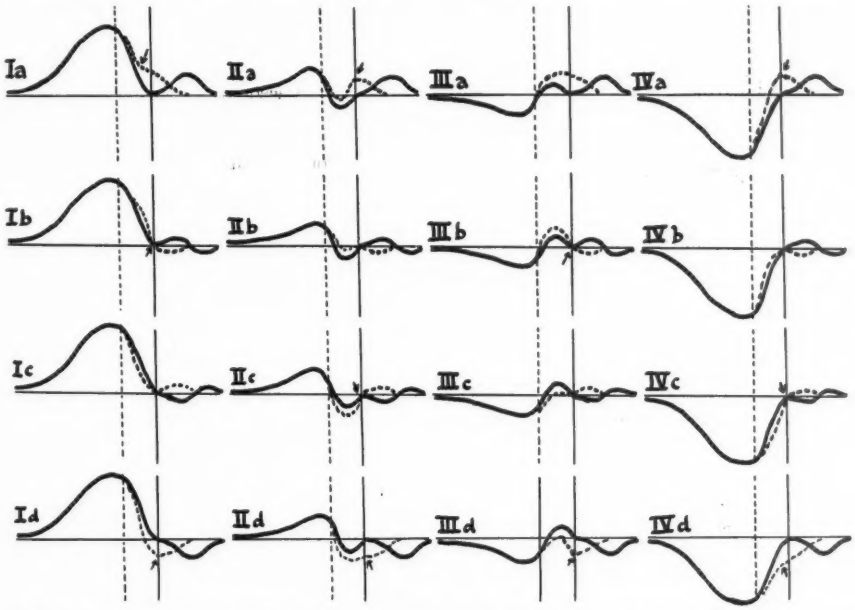

FIG. 3. Schematic representation of the sixteen possible combinations between T and U waves. Full curves: T and U waves separate. Dotted curves: T and U waves partially merged. The vertical lines indicate the end of the T wave. The arrows point to the notch or kink between T and U.

a definite kink between the ascending limbs of the T and U waves, which can be used to determine the end of T (lead V_4 in figure 5*a* of reference 14, chest lead in figure 65 of 18). If no distinct kink is present, the pattern can be mistaken for a diphasic (negative-positive) T wave; however, in such cases the distance between the nadir of the T wave and the summit of the U wave usually exceeds 35 per cent of the distance between the latter and the beginning of QRS, while in the case of a true diphasic T wave the distance between the nadir of the negative phase and the summit of the positive phase usually does not exceed 35 per cent of the distance between the latter and the beginning of QRS.

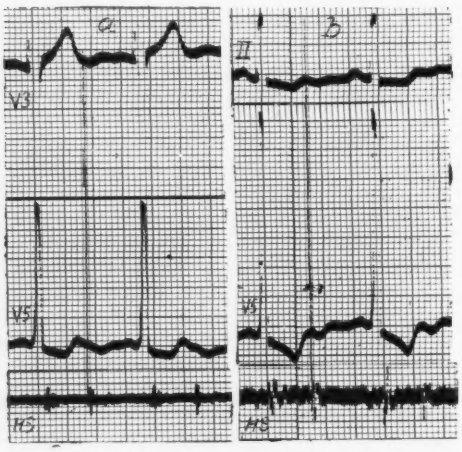

FIG. 4. Leads II, V_3 and V_5 and the heart sounds, synchronously registered, in a patient with hypertension during infusion of epinephrine. *a:* Lead V_5 shows a kink between the terminal positive phase of T and the negative U wave, synchronous with the beginning of the second sound. *b:* Leads V_5 and II show a notch between a negative T wave and a negative U wave, also synchronous with the beginning of the second heart sound.

The patterns IVc and IVd with negative T waves and negative initial portions of the U waves show always a clearly visible notch between T and U, which can be used to determine the end of T (for example, figure 4*b*, lead V_5).

5. Superposition of the U Wave on the T Wave (Merging of T and U)

The greatest difficulty in the determination of the Q-T interval is encountered when the U wave begins earlier than the end of the T wave and the two deflections are superimposed upon each other. The differentiation between the T and U waves in cases where they show merging can be facilitated by the study of the relation of these waves to the second heart sound. In multiple channel electrocardiographs the heart sounds can be recorded synchronously with the electrocardiogram on a separate channel, but even in single channel electrocardiographs which have no provision for heart sounds, the latter can be superimposed on the electrocardiogram by registering lead V_4 through a magnetic microphone (converted radio headphone) placed in the region of the great vessels.

In the great majority of normal cases the second heart sound coincides with the end of the T wave,[24] but it can precede it by 0.02 second or follow it by 0.01 second[26, 45] up to 0.12 second.[16] In a series of 1000 unselected clinical cases[18] the beginning of the second sound occurred within 0.02 second of the end of T in 86 per cent, preceded or followed it 0.02 to 0.04 second in 8 per cent and more than 0.04 second in 6 per cent. However, in this series no adequate differentiation was made between the T and U waves if these showed unusual form. In all illustrated cases where the second sound preceded the end of the T wave by more than 0.07 second[17, 18] the end of T was not clearly visible and the end of the U wave was used in measuring the Q-T duration. This was emphasized earlier.[23, 27] In other illustrated cases where the second heart sound seemed to appear as much as 0.24 second earlier than the end of T (for example, figure 257 of reference 26) the end of the T wave could also not be determined exactly and the end of the U wave was considered as the end of T. In cases with intraventricular conduction disturbances the end of T is caused by the ventricle activated with delay, and must therefore be correlated with the beginning of the second section of a split second sound. However, in right intraventricular conduction disturbances the late closure of the pulmonary valve may not cause any visible vibrations in the phonocardiogram; in this case the difference between the actual QRS duration and the average QRS duration of 0.08 second must be added to the time of appearance of the second sound.

According to our measurements on personal cases and on those published in the literature,[18, 26, 35, 46] the second heart sound always appeared less than 0.10 second (usually less than 0.07 second) before the end of the T wave, when this end could be measured exactly. In all cases without intraventricular conduction disturbances where this interval was ex-

ceeded, a merging of T and U was present and an exact determination of the end of T was not possible. Most of these cases were those of hypopotassemia. We therefore suggest consideration of every case in which the beginning of the second heart sound precedes the apparent end of the T wave more than 0.07 second as a possible case of merging of T and U. In such cases as many precordial leads as possible should be taken, since one of these leads usually reveals a clear-cut boundary (a notch or a kink) between the true T wave and the U wave. This boundary must be sought at a point in the neighborhood of the second heart sound. The repetition of electrocardiographic tracings at short intervals (sometimes as often as every few hours or even minutes) during the course of treatment usually reveals a stage where a precise separation of T and U can be made.

Each of the 16 patterns described in the preceding section can be modified by an earlier occurrence of the U wave with respect to the T wave. In figure 3 the patterns which can theoretically result from such a modification are represented by interrupted lines. A slight degree of merging may have been present in most of the examples used to illustrate the figures in the preceding section, but the point of junction between T and U was very near the base line and caused no measurable error in the location of the notch or kink in respect to the end of T.

It would lead too far to describe in detail the modifications of the 16 patterns caused by different degrees of merging of the T and U waves. In the following we shall confine ourselves to a description of some of the most commonly found patterns of merging between T and U. In the first pattern, which originates from pattern Ia of figure 3, the T wave shows only insignificant changes while the U wave shows a progressively earlier beginning, climbing onto the descending limb of the T wave. This pattern is observed especially under the influence of epinephrine and during and after physical exercise (see figure 57 of reference 24). In this pattern there is always a notch between the T and U waves; this notch can be easily recognized because of the great difference in the slope of these waves.

In order to visualize the relation of the notch between T and U in the above pattern to the end of the T wave, an enlarged tracing of the T and U waves of a normal person was made, and the U wave gradually moved to the left toward the QRS complex (see legend to figure 5). An attempt to determine the true end of the T wave in cases of partial merging of T and U can be made by drawing a tangent to the steepest descending slope of T between its summit and the notch, and by determining the point of intersection of this tangent with the base line. In figure 5*b*, this point is situated before the true end of T, which is indicated better by the nadir of the notch. In figure 5*c*, the point of intersection lies between the notch and the true end of T and designates the end of T more exactly than the nadir of the notch. In figure 5*d*, it is beyond the true end of T, but still gives a better approximation than the nadir of the notch. In figure 5*e*, the intersection of the tangent with the base line is situated far beyond the true end of the T wave, and the best approximation to the end of T will be a point halfway between the nadir of the notch and the point of intersection.

In the patterns of merged T and U waves described in the preceding pages, the T wave retained the characteristic steep slope of its descent, and a notch between T and U was always present. The only difficulty in these cases was the exact determination of the end of the T wave, whereas the presence of merging was easily recognized. In the pattern to be described in the following paragraphs, the T wave usually becomes very flat and finally inverted, while the U wave shows an extreme increase in voltage, assuming a configuration resembling that of the normal T wave and exceeding the latter in amplitude. In this pattern, which appears in its most characteristic form in cases of hypopotassemia, the U wave was very often mistaken for the T wave.

Several patterns of merging between T and U may be observed in hypopotassemia. In many cases these patterns appeared in regular sequence during the development or regression of hypopotassemia; however, due to the rapidity of these changes, only very few cases have been published in which all these patterns appeared in the same patient. In the pattern of figure 6*b*, the U wave shows elevation and the T wave is depressed, but still shows a normal

configuration and is higher than the U wave, so that no question can be raised as to the identity of the waves. This pattern corresponds to patterns IV and V of Bellet and co-workers,[4, 6, 7] who found these patterns in about 9 per cent of the cases with hypopotassemia, especially in those due to vomiting. The pattern of figure 6*c* is characterized by a further depression of the T wave and elevation of the U wave, which leads to a reversal of the normal relation between the voltage of these waves. A notch between T and U can be clearly seen, but because of the high voltage of U this wave can be mistaken for the second summit of a notched T wave (section 3). Such cases are illustrated in the following published cases: lead CF4 in figure 20 of reference 33; figures 4*A* and 5 of reference 8; figure 4*B* of reference 5; figure 3 of reference 27; figure 35*a* of reference 18.

In the pattern shown in figure 6*d*, the T wave has become so low that it forms only an insignificant notch in the ascending limb of the U wave, which has become very tall and assumed the typical form of a T wave. In other published cases no notch whatsoever is visible and the pattern, taken alone, cannot be distinguished from an unusually long T wave. In some of these cases, the pattern of figure 6*c*,

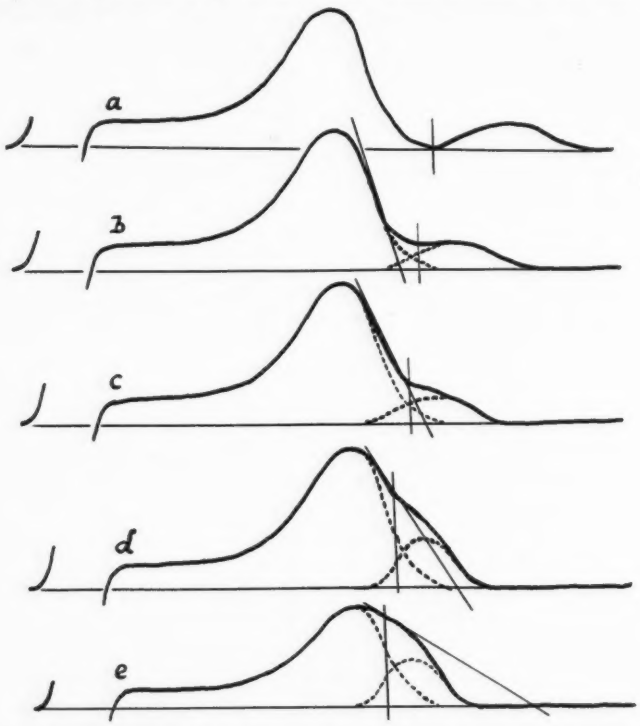

FIG. 5. *a*: Lead V_3 of a normal person, showing well developed, separated U waves. Enlarged tracing; the QRS complex is not fully reproduced. *b*: Theoretic construction of the curve which would result if the U wave occurs earlier, causing an elevation of the T-U junction which does not exceed one fourth of the amplitude of T ("first degree merging of U and T"). *c*: U occurs still earlier so that the notch between T and U is situated more than one fourth but less than one half of the vertical distance from the base line to the summit of T ("second degree merging"). *d*: U wave still earlier and twice as high; the notch appears in the upper half of the T wave ("third degree merging"). *e*: same as *d*, but T is ½ smaller; the notch advances to the upper quarter of T ("fourth degree merging"). The vertical line indicates the position of the notch between T and U. The oblique lines are tangents to the steepest section of the descending limb of the T wave preceding the notch.

with a distinct notch, or pattern *e* with a kink between T and U could be found in other leads (figure 2 of reference 12; figure 1*A* of reference 7; figure 2*D* of reference 39; figure 8 of reference 40; figure 2 of reference 29; figures 40, 42*b*, 46*a*, 63 of reference 18) but in others no such leads were registered (tracing 1 in figure 8 of reference 30; figure 37*a* of reference 18). If this pattern appears in the same patient as a transition between the patterns c and e, where T and U can be differentiated, and if the peak of this apparent T wave corresponds to the peak of the U wave in electrocardiograms taken within a short interval of time, without a major change in the heart rate (cases of figure 3 of reference 7, figure 2 of reference 5), it is almost certain that the wave in question is the U wave and not the T wave. This also becomes probable if the second heart sound begins more than 0.07 second before the end of the questionable wave (figure 91*b* of reference 19, figures 35*a*, 36, 57 of reference 18). At any rate, appearance of similar questionable TU waves in all the registered leads would require repetition of the electrocardiogram at short intervals during treatment, with registration of heart sounds and supplementary chest leads.

The pattern of figure 6*e* can be easily taken to represent a diphasic (negative-positive) T wave with a greatly prolonged Q-T interval. In most cases there is a definite kink (sudden change in the slope of the curve) between T and U, such as in the cases of figure 6*e* and figure 1 of references 11, 33, figure 1 of reference 44, figure 2 of reference 15, figure 2 of reference 21, figure 2 of reference 9, figure 38*a* of reference 18, but in other cases the transition between the negative T and U was smooth, corresponding to pattern IIb of Bellet (figure 2 of reference 33, figure 3 of reference 43, figure 93*b* of reference 19, figure 25*e* of reference 18). In these cases it is natural to consider the elevated U wave as a T wave, and a differentiation can be made only if a definite kink between T and U is present in another lead, in another complex of the same lead (figure 7 of reference 4) or at a different time (figures 2 and 6 of reference 12, figure 1 of reference 33, figure 40*a* of references 18, 34), or if the distance between the nadir of the negative T wave and the summit of the U wave exceeds that usually found between the peaks of a diphasic T wave, as discussed for patterns IVa and b in section 4. In our own cases as well as in those from the literature (figures 21, 25*e*, 26*a*, *c*, 31, 37*a*, *c*, 38*a*, 40*a*, 42*b*, 46*a* of reference 18) where the heart sounds were registered, the second heart sound actually coincided with the kink between T and U, so that assuming this point to represent the end of the T wave would certainly entail a smaller error than if the end of the elevated U wave were used to measure the Q-T duration.

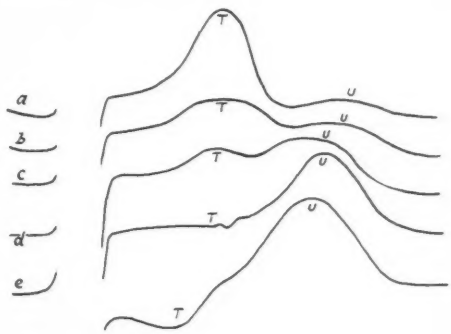

FIG. 6. Enlarged tracings of lead V_3 in a case of hypopotassemia (case 3 of P. M. McAllen[28]), taken at different times during treatment. The tracings were chosen because the heart rate was the same in all cases and the curves could be synchronized. Only the beginning and end of QRS are reproduced.

a: Serum potassium 4.6 mEq. per liter. Normal configuration of T and U. *b:* Serum potassium = 3.05 mEq. per liter. Elevation of U, depression of T. *c:* Serum potassium = 2.74 mEq. per liter. The U wave exceeds the T wave in amplitude. *d:* Serum potassium = 2.64 mEq. per liter. T wave very low, notched; U greatly elevated. *e:* Serum potassium = 2.64 mEq. per liter. T negative or diphasic (negative-positive), U greatly elevated.

As mentioned above, the elevated U wave in hypopotassemia was usually considered as a very long T wave, and this led to the widespread belief that prolongation of the relative Q-T duration is one of the most characteristic criteria of hypopotassemia. It was recognized early by one of us[23] as well as by Ljung[27] that in many published cases where such a prolongation was found, the Q-U interval was measured instead of the Q-T interval. Bellet

and his group, [4–7, 30] who must be credited with the most comprehensive study of the ECG in hypopotassemia, saw many cases in which consecutive cycles of the same lead showed transitions between an apparently long Q-T interval and a T wave of normal duration accompanied by an elevated U wave. That the elevation of the U wave is a more specific sign of hypopotassemia than changes of the T was shown by the observation of Bellet and co-workers that after medication with potassium salts the U wave disappeared with but little change of the T wave. McAllen[28] pointed out that the broad and deformed T waves seen in cases of hypopotassemia are similar in form and position to well defined U waves which appeared in the same patients and in the same leads within short intervals of time; he therefore came to the conclusion that the Q-T interval proper is not characteristically prolonged in hypopotassemia. If the inverted waves which precede the elevated U waves in cases of marked hypopotassemia are to be considered as T waves, a definite shortening of the relative Q-T duration must be postulated. This agrees with the shortening of the interval between the Q wave and the beginning of the second sound.

Bellet and co-workers recommended that the Q-T duration and the Q-U duration should be used interchangeably in the diagnosis of hypopotassemia, since they considered the U wave as well as the T wave as part of the electrical systole. This seems to us not justified as the U wave occurs in all cases after the end of the second heart sound and therefore during hemodynamic diastole. If Q-T and Q-U were used interchangeably, the corrected Q-T duration would appear prolonged even when hypopotassemia is not present, as a U wave is present in at least one lead in almost all cases. At any rate, the designation of "relative Q-T duration" implies explicitly that it is the T wave and not the U wave which is being measured. It seems imperative to us that in any evaluation of the relative Q-T duration it should always be stated explicitly whether the Q-T duration or Q-U duration was being measured, and that cases where an adequate separation of the two waves could not be made should be clearly indicated as such. According to our experience, the error entailed when a notch or kink between the T and U waves is considered as the end of the T wave is much smaller than when the end of the U wave is used to measure the Q-T duration; this error is the smaller, the nearer the base line and the further away from the apex of T these notches or kinks are situated.

6. Superposition of Auricular Complexes on the T Wave

Fusion of the T wave with the P wave is common in A-V conduction disturbances, in A-V dissociation and in supraventricular extrasystoles. In cases where all T waves are merged with P waves there may be a considerable difficulty in the determination of the Q-T interval. In the cases where the shape of the P wave is known (for example, in 2:1 A-V block), it can be geometrically subtracted from the area of the merged T and P wave; this would give us the true shape of the T wave. In many cases of supraventricular tachycardia T and P cannot be properly separated as the transition between these waves is continuous. In all these cases the left precordial leads V_{4-6} can be best used for the determination of the end of T, as the voltage of P in these leads is usually very small. This applies also to superposition of auricular fibrillation and flutter waves on the T wave.

Summary

1. The difficulties and sources of error in determination of the beginning of QRS and the end of the T wave are classified and analyzed.

2. The beginning of the QRS complex and/or the end of the T wave may be isoelectric in some of the leads. If a number of leads can be registered synchronously, the Q-T duration should be measured from the earliest point of QRS to the latest point of the T wave; curves of the three standard or of unipolar limb leads can be synchronized even if they were not registered synchronously.

3. In fusion or merging of the end of T with an elevated U wave, the merged T + U complex is usually mistaken for a notched or diphasic T wave of bizarre configuration. A simple method of differentiation between these two

forms is based on the fact that the distance between the summits of a notched or diphasic T wave almost never exceeds 35 to 40 per cent of the distance between the beginning of QRS and the second summit, while the distance between the summits of T and U exceeds this percentage of the distance between QRS and the summit of U. In most cases a notch or a kink is present between T and U, especially in the precordial leads V_2 and V_3. This point is usually situated within 0.04 second of the beginning of the second heart sound; it indicates the end of T the more precisely, the nearer to the base line and the further away from the summit of the T wave it is situated.

4. The measurement of the end of an elevated U wave instead of the end of T has caused the erroneous conclusion that the corrected Q-T duration is prolonged in many published cases of hypopotassemia and in some cases after physical exercise. If the criteria outlined in this paper are applied, the true corrected Q-T duration is not increased or is even shortened in typical cases of hypopotassemia without hypocalcemia.

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The Nickerson Ballistocardiogram in Arteriosclerotic Heart Disease with and without Congestive Failure

By RICHARD J. JONES, M.D.

Comparison of ballistocardiograms in patients with arteriosclerotic heart disease with those of normal subjects, young and old, with regard to the various time relationships of the I and J waves, as well as the IJ amplitude, reveals increasingly frequent abnormality in age as compared with youth, in arteriosclerotic heart failure as opposed to heart disease. Certain characteristics of the ballistic pattern in heart failure are noted, and these are modified to some extent by therapy. Serial studies indicate a peak increase in ballistic amplitude with diuresis which may not be sustained.

THE LOW-FREQUENCY ballistocardiogram introduces a new degree of precision in the early recognition and appraisal of arteriosclerotic heart disease and may aid in evaluating subsequent heart failure and its treatment. The ballistocardiograph has already been proposed as a simple tool for the purpose of screening such potential patients.[1-3] Thus far, however, Starr[1] has confined his discussion to alterations in amplitude and gross form in the high-frequency ballistocardiogram, while Brown and de Lalla[3, 4] have recently added an index, based on the variations in amplitude with respiration, to supplement the grosser abnormalities. Serial observations on patients in heart failure have previously been reported,[5, 6] but no consistent pattern of improvement was presented.

MATERIAL AND METHODS

The patients were selected from the wards of Albert Merritt Billings Hospital and the Cardiac Clinic of the University of Chicago Clinics. Their selection for the groups to be studied was as follows: group 1 is a series of 40 young normal adults under 37 years of age and group 2 is a series of normal patients older than 37 with criteria as previously described;[7] group 3 consists of 54 patients ranging in age from 30 to 72 years (average age 54), with arteriosclerotic heart disease, chosen on the basis of criteria established for the anginal syndrome or a recent myocardial infarction by the New York Heart Association; and group 4 consists of 27 patients in congestive heart failure, averaging 59 years (41 to 79 years). The tracings for group 3 were taken on outpatients or after an average of 32 days of bed rest following the onset of an acute myocardial infarction. The infarction was not fresh, and congestive failure was not and had not been present in any members of the group. Group 4 patients in congestive heart failure were likewise not in serious condition, for low-frequency ballistocardiograms cannot be taken if the patient is too dyspneic or presents a marked arrhythmia.[8] Evidence for heart failure was based upon a history of paroxysmal nocturnal dyspnea or a history of exertional dyspnea associated with basal rales, peripheral edema and/or a palpable liver. They were admitted to the series if, after treatment with digitalis, diuretics and bed rest, a weight loss of more than 2 Kg. accompanied subjective improvement, except for three instances where definite relief of clear-cut paroxysmal nocturnal dyspnea was the only indication of response. Four had a history of previous angina pectoris or myocardial infarction, but 20 presented a moderate hypertension in association with the heart failure. All patients except nine in group 3 and eight in group 4 were male.

Nineteen patients from group 4 had observations made both before and after treatment, as did five additional cases of hypertensive or mitral valvular rheumatic heart disease also in heart failure. Of these 24 cases, six had sufficiently frequent observations to allow conclusions regarding the pattern of their response to therapy. Control studies were made on normal subjects and cardiac patients not in failure, who had duplicate runs taken at intervals of several days to several weeks, to obtain some idea of how much variation might be expected in such comparisons where no failure or treatment was featured.

Ballistocardiograms of the low frequency, critically damped variety[8, 9] were taken and measured as usual,[7] in the basal state. The Q-I, Q-J, I-J and Q-K intervals were averaged for 10 complexes during apnea and tabulated. Tests for parallax on the time

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ordinate revealed that the ballistocardiographic light beam appeared to be 0.047 seconds ahead of the string shadow, and corrections of this magnitude have been made throughout. The vertical amplitude of IJ was measured in millimeters, converted to grams by the calibration factor and tabulated as *F*. Reference to the wave amplitude is just as adequate for descriptive purposes as any more elaborate calculations and denotes the maximum force mustered during systole for the headward recoil. The intervals and the maximum systolic force were tabulated, the means and standard errors calculated for each group and the results compared in detail.

Basal oxygen consumption was determined when possible in the group 4 patients with the Benedict-Roth apparatus, after taking the ballistocardiograms. Occasionally these patients had Cheyne-Stokes respiration which permitted apnea runs free from the chief objection to voluntary breath-holding. Otherwise measurements were made during normal breathing, but dyspnea made interpretation of the breathing runs impossible in seven cases. The duplicate apnea runs sometimes had complexes of different form, apparently depending upon the position of the diaphragm, the amount of straining, and the fatigue of the heart. It was also noted on a few occasions that short intervals between periods of breath-holding caused the amplitude to grow smaller. This effect was avoided for the most part by waiting at least five minutes between breath-holding runs.

The treatment in the group 4 patients varied from digitalis (Digilanid) alone in six patients who were treated in the outpatient department, to bed rest, Digilanid, often with mercurial injections (Thiomerin) and supplementary ammonium chloride, and various sedative agents in the remainder of the patients, who were hospitalized for periods of 7 to 30 days. Diuretic response to therapy was one of the criteria for selection of these patients but all showed clinical improvement as well.

Results

The comparisons between the four groups can best be made by studying the relative distribution of the various intervals, and the amplitudes, as indicated in figure 1.

The Q-I duration, as limited in young normal subjects between 0.18 and 0.24 second, is exceeded slightly in both directions in the older (patient) series. In patients with arteriosclerotic heart disease the spread is further emphasized, and in heart failure a bimodal type of distribution is seen, with all but a few cases outside of the normal range. The tendency for a shorter Q-I interval with older age seems to be partially reversed as the myocardial process progresses, so that with a good many of the hearts sufficiently effected to produce failure, grossly prolonged Q-I intervals are found.

The Q-J duration also shows increasing dispersion with age and with disease, with a greater tendency to shorten in group 4 than is manifested by the Q-I interval.

The I-J duration, also is seen to show greater spread with age, and still further with disease. There is no tendency for it to increase, however, but a definite tendency for it to shorten. Again, a bimodal distribution is seen in heart failure. The mean I-J interval is not significantly different between groups 2 and 3 (table 1), though it is significantly shorter in the failure group.

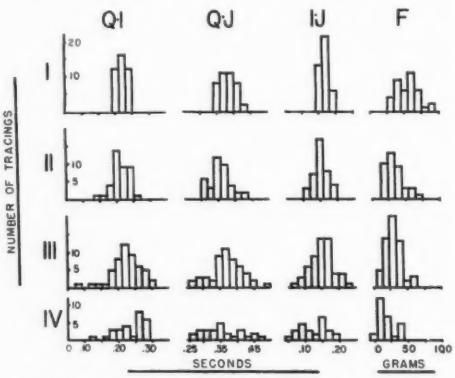

FIG. 1. The distribution of the Q-I, Q-J, and I-J intervals and the IJ amplitude corrected to grams (*F*) in the four groups under discussion. The shaded bars indicate the number of ballistocardiograms in each category falling outside the range established by the young normal group.

The Q-J/Q-I ratio was compared in all groups. There was no significant change between the two normal groups, or either normal group with the patients with coronary artery disease. The group in heart failure, however, had a significantly reduced ratio, as would be expected if Q-J remained relatively constant while Q-I lengthened. Because of the high proportion of the failure group having hypertension, the Q-J/Q-I ratio was derived from the series of hypertensive patients not in failure, reported previously.[7, 10] This class of subjects presented a mean ratio much higher than even the normal groups, because of the inordinately short Q-I intervals. Thus, the reduced ratio in failure becomes even more significant, inasmuch as it

exists even though the great majority have hypertension. There is a wide range of values and considerable overlap between the various groups so that diagnostic value cannot be attached to this figure.

A statistical comparison of various mean values in the four groups under discussion is presented in table 1. The reduction in mean values for Q-J, I-J, Q-K, and *F* between groups 1 and 2 are all significant statistically (p less than 0.01). There are no significant differences between means of groups 2 and 3, but I-J and *F* are both reduced between groups 3 and 4 (p less than 0.01), and Q-I is lengthened between groups 2 and 4. All the differences of group 4 from groups 2 or 3 are even less than those between hypertensives and group 4.

The maximum systolic force, F, shows progressive reduction with age and with progress of the disease process in figure 1. There is no significant difference between mean values of *F* for the older normals and the patients with arteriosclerotic heart disease. In failure, *F* is markedly reduced, except in a few instances. This reduction is repaired to some extent following treatment. The mean value (table 2) is significantly lower statistically (p less than 0.01) than that for the patients with arteriosclerotic heart disease (without failure), a group of hypertensive patients not in failure, or either normal group. Because a reduction in *F* with a corresponding increase in pulse rate might indicate no real change in minute force induced by the heart, the grams force (*F*) multiplied by the pulse rate (*P*), hereafter called the minute systolic force, was also calculated for the various subjects. As can be seen from table 1, the same differences in amplitude persisted even after this factor was included, for the basal pulse rate was not greatly elevated in the particular subjects we were able to work with.

Deviations from the normal form have previously been defined only by notching, slurring, or bizarre alterations in amplitude of one wave or another. We feel our results indicate that much better criteria may be at hand in the normal standards of amplitude and certain of the intervals applicable to the low-frequency in-

TABLE 1.—*Mean Values and Standard Deviations for the Various Time Intervals and IJ Amplitudes for Each Group of Patients**

	Q-I	Q-J	Q-K	I-J	*F*	(*F* × *P*)
	sec.	*sec.*	*sec.*	*sec.*	*Gm.*	*Kg./min.*
Group 1	.213±.015	.375±.023	.581±.036	.162±.013	53.7±14.5	3.7299±1.090
No. of patients	40	40	40	40	40	40
Group 2	.203±.025	.351±.031	.541±.037	.149±.020	34.1±13.0	2.5514±1.046
No. of patients	39	39	39	39	39	39
Group 3	.215±.044	.364±.044	.548±.039	.148±.031	30.1±11.7	2.181±1.086
No. of patients	51	51	51	56	57	57
Group 4	.224±.045	.345±.063	.528±.067	.118±.039	18.6±11.4	1.400±0.721
No. of patients	27	26	24	26	27	27

* Group 1 and 2 values are in agreement with those previously reported[9], if they had been corrected for parallax.

TABLE 2.—*Number of Tracings in Each Group Falling within the Mean Value ± 2 Sigma for the Indicated Intervals, as Derived from the Two Normal Groups*

Patient Group	Total No. of Patients	Normal by Criteria I		Normal by Criteria II	
		No.	*%*	*No.*	*%*
1	40	40	100	40	100
2	39	18	46	35	90
3	51	17	33	26	51
4	27	2	7	6	22

Criteria	*I*	*II*
Q-I range	.18–.24	.15–.25
Q-J range	.33–.42	.29–.41
I-J range	.14–.20	.105–.185
F minimum	<25.0	<20.0

strument. While some slurring can be seen in normal subjects, frank notching with respiration arrested has been seen by us only in patients with frank heart disease or anemia (fig. 2). Notching or marked slurring was noted in 15 of the 57 cases in group 3 (fig. 3), in 11 cases of the 27 in group 4 (fig. 4), but was not

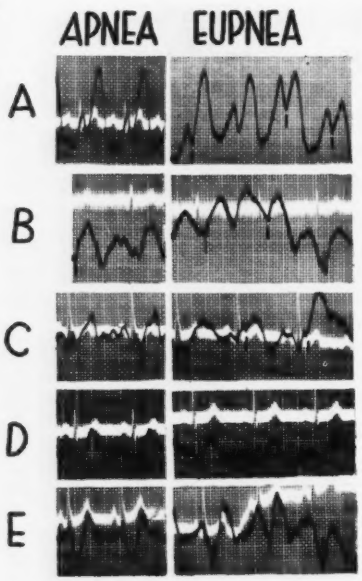

FIG. 2. Some variations in degree of notching and/or slurring in patients with apparently normal hearts. I waves are labeled as necessary. The electrocardiogram shown is lead II. (A) A 19 year old patient with ulcerative colitis; 10.0 Gm. hemoglobin. (B) A 34 year old female, thoroughly investigated; only positive finding was anemia, 11.0 Gm. hemoglobin. (C) A 47 year old male with duodenal ulcer history and recent melena; 11.0 Gm. hemoglobin. (D) An 85 year old male; no demonstrable disease, but pipestem arteries. (E) A 56 year old male with no organic disease; note broad, slurred I wave; presence of H wave is questionable.

seen in cases of group 1 or, expecting those illustrated in figure 2*d*, *e*, of group 2.

Table 2 indicates the percentage abnormality, depending upon the strictness with which we draw the limits of normal, using the finer criteria for normality. The two diseased groups are compared with the normal groups, the range of normal is selected as the mean $\pm 2\sigma$, using values derived from the group 1 normals in the first column, from group 2 normals in the second column. Using the broader of these criteria for delineating normal cases, it can be

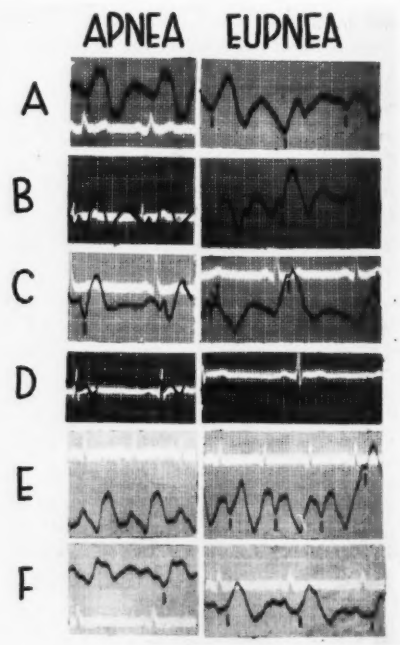

FIG. 3. Illustrative ballistocardiograms from group 3, cases of arteriosclerotic heart disease. (A) Angina patient who subsequently sustained an infarction; note notching of J and K waves, not uniformly present in breathing run. (B) Angina patient with very atypical history; completely normal ballistocardiogram; succumbed to fatal coronary occlusion (autopsy) five hours after recording. (C) Myocardial infarction four weeks old; note prolongation of Q-I in apnea, obscured by slurring in the breathing run. (D) Myocardial infarction at age 72; patient expired suddenly nine months later; note delay and possible notching of I and notching of J, plus low amplitude. (E) Myocardial infarction, age 43; note relatively normal tracing in apnea, with an abnormal early headward wave appearing inconstantly in eupnea. (F) Myocardial infarction four months previously; note notching of J wave in apnea, and slurring of I wave which is enhanced during respiration; note low amplitude of IJ.

seen that at least 50 per cent of the patients with clinically established arteriosclerotic heart disease and 78 per cent of patients with heart failure have one or more values beyond the range found in asymptomatic subjects of com-

parable age for Q-I, Q-J, and I-J or *F*. Of nine patients in group 3 with electrocardiograms found to be within normal limits, only three had abnormal ballistocardiograms, using these criteria.

The wave pattern in heart failure was strikingly different in 19 of the 27 cases by the presence of an abnormal H wave. It is a headward movement of the table, starting with or very soon after the QRS complex of the electrocardiogram, reaching a height frequently greater than the J peak, and falling to make an I valley. This is comparable probably to the "early M" complex of Starr.[11] We have not encountered it, however, in other circumstances than heart failure, and with return of compensation it disappears in the majority of cases, or remains in modified degree. The delayed I wave, which frequently occurs in heart failure is not necessarily correlated with the presence of this abnormal wave, and, when present together, recession of the abnormal H wave is not accompanied necessarily by a shortening of the Q-I interval. The rise may merge indistinguishably with the ascending limb of the preceding K wave, and it may obscure the I wave completely, the J wave occurring as a notch on the descending limb of this wave (fig. 4*c*). It seems to be more marked in the presence of hypertension, but occurs with a normal blood pressure as well. In fact, the recognition of I and J waves was possible, in a few cases, only after following the patient with serial tracings until compensation returned and the abnormal wave receded. It has occurred to us that the same abnormal early systolic wave may explain lesser abnormalities in the I wave, such as reduced amplitude, or slurring, which is often present in failure.

Variations of this wave, as seen in heart failure patients, are presented in figure 4. When present, the patient was in undeniable congestive heart failure, so that this finding could hardly be said to be of diagnostic value in early or questionable failure. However, we have not encountered it in our experience except in this condition during the apnea run. One patient in group 3 had occasional complexes during quiet breathing, which might have been considered to be abnormal H waves (fig. 3*d*), though these are inconstant, varying with the phase of respiration.

The respiratory variation in *F* has been proposed as a measure of abnormality universally present in patients with angina pectoris.[3] We reviewed our tracings taken during ordinary respiration in an effort to compare the variation

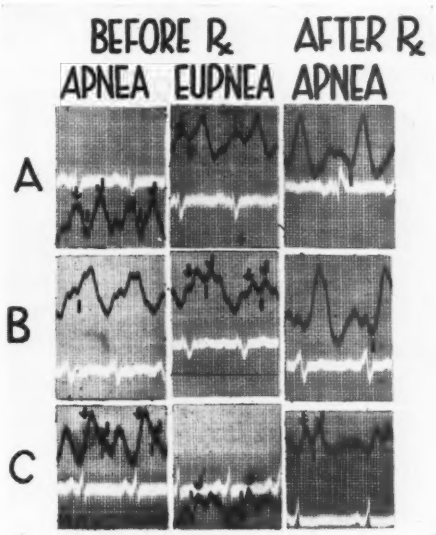

FIG. 4. Ballistocardiograms taken during congestive failure during breathing and apnea, compared with tracings taken after therapy. All patients were hypertensive and all showed dramatic improvement with therapy. (Calibration is unchanged in each row across.) (A) Note abnormal H waves, more marked in apnea, absent after therapy. (B) Tremendous variation between breathing and apnea before treatment, abolished with therapy. Possible H wave is indicated (by arrow) in breathing run. Dramatic increase in amplitude of IJ (*F*) with improvement. (C) Huge H wave (see arrow) obscures IJ complex, which becomes a slurring on descending limb, clarified by breathing run; note substantial residual H wave after therapy.

in amplitude of IJ, presumed to be respiratory in origin. We had originally made no effort to measure the phase of respiration, so simply chose maximal and minimal values of *F*. The maximal (inspiratory) amplitude is above twice that for the minimal (expiratory) amplitude in only three of the normal subjects in group 1. In group 3, 45 patients had tracings taken during quiet respiration, which could be com-

TABLE 3.—*Number of Cases Presenting Increased Variation in Maximum Systolic Force (F) with Respiration in the Older Age Group, with (Group 3) and without (Group 2) Clinical Arteriosclerotic Heart Disease*

Patient Group	No. of Patients	Max F/Min F > 2	Max F/Min F > 3
2	35	18	7
3	45	20	7

TABLE 4.—*The Improvement in Maximum and Minute Systolic Force and the Ratio of Oxygen Consumption to Minute Systolic Force in Patients Treated Successfully for Heart Failure*

Name	Before Therapy		Interval	Percentage Change Following Therapy		
	Maximum systolic force (F)	Minute systolic force ($F \times P$)		Maximum systolic force (F)	Minute systolic force ($F \times P$)	Oxygen consumption/ ($F \times P$)
	Gm.	*Kg./min.*	*days*	%	%	%
*Ho	14.3	1.26	41	+107	+78	
Pi	39.0	1.80	9	+10	+20	−30
Ma	16.6	1.59	6	+212	+133	−63
Ka	16.1	1.45	10	+105	+56	−35
Fo	18.1	1.59	10	+81	+21	−40
Br	12.3	1.30	20	+148	+25	−51
*Mu	18.3	1.08	104	0	−7	−33
Bu	15.0	1.26	10	+13	+9	
*Sh	26.2	2.28	9	+50	+26	−31
Iv	2.8	0.24	6	+214	+230	
Di	13.6	1.30	3	+79	+29	−33
Wi	21.0	1.30	8	+13	+33	−16
Me	20.2	1.54	10	+26	+14	−17
Dj	34.7	2.15	26	+4	+3	−6
*Ra	29.8	1.73	16	+39	+37	−27
Hi	28.4	2.04	6	+29	+11	−17
*Ha	9.9	0.81	8	+93	+72	−53
*Ro	17.8	1.28	52	+68	+78	−37
Ap	8.4	0.80	9	+114	+59	−52
Va	3.0	0.22	7	+605	+810	
He	14.9	1.34	4	+112	+69	
Ka	6.3	0.38	10	+229	+133	−61
Br	9.8	0.82	6	+125	+114	−56
Mo	6.4	0.44	9	+427	+234	−74
Average	16.6	1.23	16.6	+121	+94	−38
Standard error				±29	±34	±5

* Outpatients: received digitalis therapy only.

pared for respiratory variation with 35 of the group 2 normals of comparable age (table 3). In the latter cases, 18 presented maximum F/minimum F ratios greater than 2.0, and seven cases had ratios as high as 3.0. In the patients with angina or infarction, 20 presented maximum F/minimum F ratios equal to or greater than 2.0, and seven had ratios greater than 3.0. The difference between these two groups is not significant by the chi square test.

In a comparison before and after treatment of certain patients in group 4 the percentage change in the maximum systolic force (F grams); the pulse rate; their product, or the minute systolic force ($F \times P$ kilograms per minute); and the ratio of oxygen consumption to ($F \times P$) are presented in table 4. As can be seen, there was a fairly universal fall in pulse rate with improvement, though all but two of these patients had a sinus rhythm. There was a marked tendency to increase the IJ amplitude (F), though in five patients the increase was less than 20 per cent and probably not significant. The reduction in pulse rate did not compensate for the increase in maximum systolic force (F), for the average minute systolic force ($F \times P$) was also increased to just about twice its value before treatment. If further account is taken of the oxygen consumption, so that the simultaneous body requirement for cardiac work is considered, the change becomes still more significant, for in certain subjects who had hardly significant changes in amplitude, a great reduction in oxygen consumption indicated that an increase in cardiac force relative to the requirement was actually present. The ratio of oxygen consumption to ($F \times P$) has the same sense as the A-V oxygen difference, and the failure value was reduced 38 per cent by treatment. Of the 19 cases in which oxygen consumption determinations were available before and after, all but three cases showed a probably significant (more than 20 per cent) reduction in this ratio.

Fifteen of the 20 with abnormal forms could be said to have changed toward normal with clinical improvement, as remarked by Mathers and co-workers.[6] One difficulty imposed by the low-frequency instrument is the destruction of any recognizable pattern by dyspnea. In 17 of these 25 subjects, slow breathing records were available and calculable (four of these presented

TABLE 5.—*Variations of Systolic Force in 27 Paired Observations, Separated by One or More Weeks, in 17 Control Subjects Not in Heart Failure*

Runs Selected for Comparison	Average Percentage Change	
	Maximum systolic force (F)	Minute systolic force ($F \times P$)
	%	%
First eupnea run	+0.8	+5.5
Standard error	±4.1	±5.8
Average of two eupnea runs	+4.5	+2.8
Standard error	±4.7	±5.5
Average of two apnea runs	+5.8	+10.0
Standard error	±4.4	±6.6

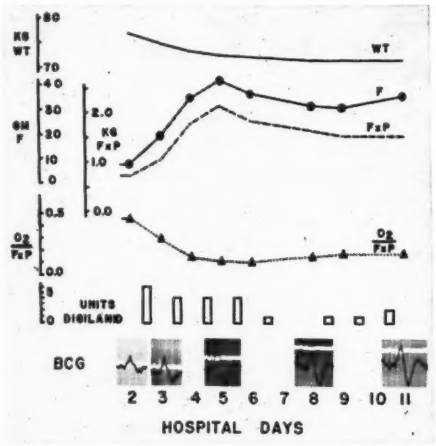

FIG. 5. A 67 year old man with hypertensive arteriosclerotic heart disease and marked congestive failure. Note the two- to threefold increase in amplitude of IJ during the maximum diuresis (indicated by weight loss), which levels off at an intermediate level on maintenance digitalis. The oxygen consumption falls concurrently. The ballistocardiogram can be seen to increase in amplitude and improve in form.

The solid line represents body weight (WT) in kilograms; the solid line with heavy dots represents maximum systolic force in grams (F) as derived from the IJ amplitude; the dashed line indicates kilograms per minute of systolic force ($F \times P$); and the dotted line, with triangles indicating observation points, represents the ratio of oxygen consumption to minute systolic force in liters per kilogram. One unit of Digilanid is 0.00033 Gm. and the number of units given per day is indicated by bars. Representative tracings showing the ballistocardiogram during Cheyne-Stokes apnea are shown above the indicated hospital day, and the I wave is indicated where necessary.

Cheyne-Stokes respiration with involuntary apnea); the remaining eight cases required voluntary suspension of breathing for usable records. Duplicates were used in most of these eight cases, but statistical analysis of the control series established the fact, which one might guess from the crudity of the calculation and its anticipated variability, that averages of duplicates compared on different days gave hardly better comparisons than if single values were used. This was also found to be true by Paine and Shock.[12]

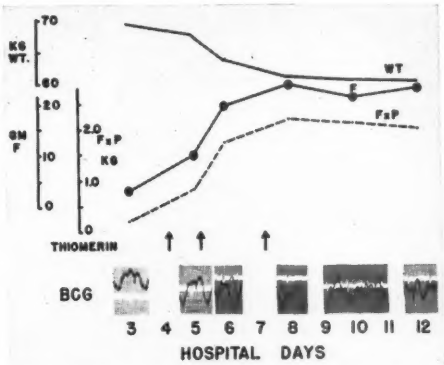

FIG. 6. A 63 year old man with arteriosclerotic heart disease admitted in his fourth episode of congestive failure on a maintenance dose of Digilanid who was treated by bed rest and morning injections of subcutaneous Thiomerin (indicated by arrows). Note that the abnormal H wave of failure dominates the original ballistic complex, yet the pattern reverts to normal in the last tracing. (See figure 5 for explanation of symbols.)

Controls. Comparison of amplitudes measured from the same subject on different days, are seen in table 5, for a group of normals and nonfailure cardiac patients (17 in number). There were observations on 54 different days for 27 duplicate comparisons. Obtaining the ratio of mean difference to the standard error of the mean difference between patients and controls, we find a highly significant difference (p less than 0.01), whether breathing records, single or duplicate, or apnea duplicates averaged were used in estimated control values.

Results of Serial Studies. Serial studies have been made on 12 patients treated in the usual fashion for heart failure, of which the most

striking examples are presented here. We are fortunate in that these six cases had a sufficient element of Cheyne-Stokes respiration to permit the exclusive use of breathing records. No voluntary apnea was required in any of the cases presented.

In all cases, thus far observed, relief of congestion, as indicated by diuresis and weight loss, was accompanied by an increase in the resting ballistic amplitude or minute stroke force (F). The maximum amplitude was achieved approximately with maximum diuresis and then yielded usually to a somewhat lower level (fig. 5), sometimes no higher than the original pretreatment level (fig. 8). This seemed to be true whether diuresis is induced by digitalis (figs. 5 and 8) mercurials (figs. 6 and 7) or both (fig. 9). If the congestion was at first relieved by bed rest or other treatment, digitalization even to the point of mild toxicity neither increased the amplitude nor improved the form of the ballistic pattern (fig. 10). Even though the posttreatment minute systolic force was no higher than the original, there was always a reduction in oxygen consumption/$F \times P$ as observed in table 4.

It can be seen from the figures that the ballistic form changes progressively from day to day as treatment continues. The huge, abnormal H wave seen in advanced cases of myocardial insufficiency, will disappear. Frequently, the I wave, slurred or rounded presumably by the same abnormal wave, will become more prominent so that a sharp and usually deeper nadir is present. Notching of the J wave may clear up (if the failing ventricle is restored to normal) or it may grow deeper as the over-all amplitude of the IJK complex is increased. Deep K waves usually remain so, but in a few instances we have noticed a reduction in depth of the K wave with improve-

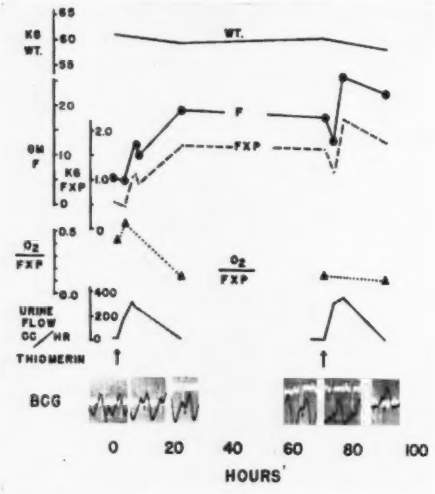

FIG. 7. A 60 year old Negro with hypertensive and arteriosclerotic heart disease who responded poorly to digitalis was given two intravenous injections of mercurial diuretic, 72 hours apart, had the urine output followed as well. Note that the maximum F developed well after maximum diuretic effect following the first injection, though it fell somewhat from the maximum F achieved during maximum diuresis, following the second injection. Again the ballistic form becomes normal with compensation though the H wave predominated originally. (See figure 5 for explanation of symbols.)

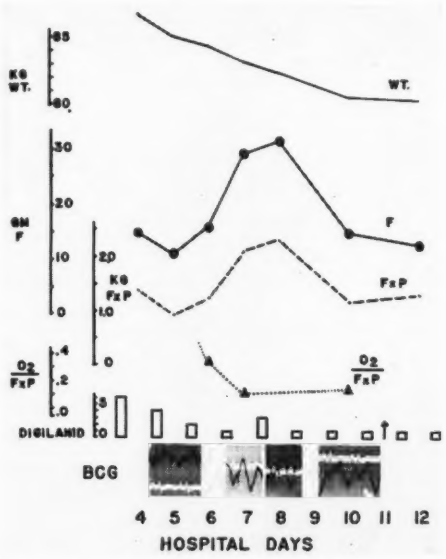

FIG. 8. A 64 year old man with only symptoms of exertional dyspnea and mild ankle edema, but a heart 40 per cent oversize, who was digitalized. Note that after increasing threefold the systolic force returned to pretreatment levels once diuresis was completed. The dyspnea and oxygen consumption were both decreased, however, and the ballistic form improved. (See figure 5 for explanation of symbols.)

nent. (See figure 7.) There is nothing unique or diagnostic about most of these changes.

Discussion

While we have demonstrated that the number of subjects presenting one or more abnormalities in the intervals discussed or an abnormal reduction in maximum systolic force increased in comparing youth to age, age to

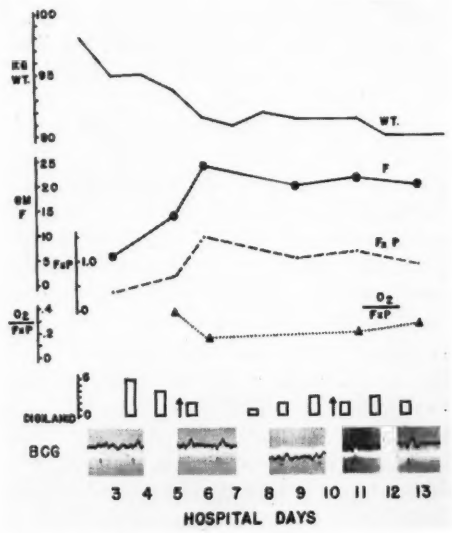

Fig. 9. A 63 year old man recently recovered from a myocardial infarction had mild symptoms of congestive failure occur as he attempted increased activity. Basilar rales, hepatomegaly and ankle edema subsided with diuresis as induced by Digilanid and augmented by Thiomerin. The two maximum values recorded for F occurred 24 hours following each mercurial injection. Note the initially low amplitude of the ballistocardiogram and the delayed I wave. (See figure 5 for explanation of symbols.)

disease, and disease to ultimate heart failure, one difficulty of interpretation lies in differentiating among abnormalities due to the relatively benign aging process, the thickening and altered elasticity of the great vessels, and actual myocardial abnormalities.[13] We have previously noted shortening of the Q-I interval in old age. This shortening is enhanced by essential hypertension,[10] presumably because of an increased elasticity of the distended aorta, but perhaps also because of a shortened maximum ejection phase. With myocardial insufficiency there is a prolongation of the Q-I interval, in general, so that a weakening myocardium in a hypertensive might well modify a previously shortened Q-I interval so as to bring it within or beyond the normal range. This explains why many of our hypertensive patients in heart failure may present a short or

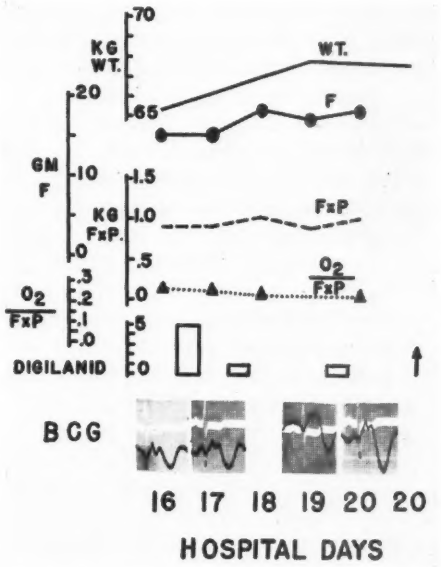

Fig. 10. A 62 year old hypertensive male with arthritis, epigastric discomfort and hemorrhoids in addition to nocturnal dyspnea, inconstant basal rales, cardiomegaly and hepatomegaly.

During bed rest for 14 days, he lost 5.7 Kg. body weight as well as his findings of congestive failure. Digitalization was then inaugurated, to be stopped after 6 units of Digilanid because of anorexia, extrasystoles and bradycardia (44 per minute). Note the absence of any significant change in $F \times P$ or in the ballistic form. (See figure 5 for explanation of symbols.)

normal Q-I interval in spite of the relatively prolonged maximum ejection phase of heart failure. The Q-J or I-J in this circumstance may be likewise shortened or lengthened but to a lesser degree, depending upon the combined effect of great vessel elasticity, the duration of the maximum ejection phase, and perhaps other factors.

A shortening or lengthening of the maximum

ejection phase, with other things unchanged, produces a rise or fall in the Q-J/Q-I ratio. The Q-J interval would seem to be related more to total volume of ejection or the duration of the total ejection phase of systole, for the J peak is generally felt to indicate the point at which predominantly footward acceleration in the descending aorta yields to deceleration. This point will be earlier in the cycle as the initial acceleration is increased, the pulse-wave velocity is increased, or the total stroke volume is decreased. Presumably, in congestive failure the numerator of the ratio, or what might be considered the interval related to stroke volume, tends to decrease, while the denominator, the time interval related to acceleration, tends to increase, and the combined effect is a decrease in the ratio. This is an admittedly sketchy hypothesis, based on the work of Hamilton.[14]

Inasmuch as the abnormal H wave of failure begins with the onset of QRS, it may be related to auricular contraction or the isometric phase of ventricular contraction. It may be due to a venous wave traveling in the congested vena cava or to the shift of the heart's position during isometric contraction, as suggested for the origin of the normal H wave,[11, 15] but this has yet to be determined experimentally. Both Starr[5] and Mathers, Nickerson and co-workers,[6] present tracings illustrating this same abnormally huge H wave. The latter group did not feel that this was significantly outstanding to deserve mention and Starr presumably categorized these as "early M" type complexes,[11] which did not particularly relate to heart failure. Although instrumental differences cannot be ignored, we have been impressed with the occurrence of this abnormality, during apnea runs particularly, in the failure group, and its great modification, if not abolishment, after successful treatment of the congestion. Cardiac patients, who have recovered from congestive failure, may still present grossly abnormal H waves.

Notching of I or J waves may very well be due to an asynchrony between the two ventricles—not necessarily an asynchrony in onset of their systoles, but an asynchrony between their two velocity curves of systolic ejection.[11] While this is a fairly well established indication of an abnormal ballistocardiogram,[1-4, 11, 16] we feel that there are definitely abnormal tracings evident only in the relative delay of I or J peaks. Using notching as the sole criterion, abnormalities were found in about 25 per cent of group 3, while application of standard limits for a normal group of comparable age brought out abnormalities in approximately 50 per cent. In group 4 alone, abnormalities were present in at least 78 per cent by our standards, whereas only 40 per cent showed significant notching. Furthermore, we have found that notching can occur with mild anemia in the absence of demonstrable underlying heart disease.

The increased variation in the amplitude of IJ with respiration in patients with angina pectoris, observed by Brown and co-workers,[3] is of interest, though these authors did not describe their "normals." In comparing our normal patients with a group of patients of comparable age with arteriosclerotic heart disease, we find that a fair percentage of both exceed the upper limit of normal for young adults in this regard, but it is not even half, much less all, of the angina and infarction patients who are thus abnormal, and the frequency is no lower in normal subjects of the same age. There seemed to be no striking correlation between this ratio and the other criteria for abnormality. In any event, there is a great overlap between normals and patients in this regard, so that such sweeping conclusions as have been made by these authors are hardly warranted from our data.

The ballistocardiograph does not measure accurately the cardiac output, though there is good reason to believe that gross changes in cardiac output will be reflected by changes in the ballistic amplitude in normals.[8, 14] The form of the velocity curve of systolic ejection presumably contributes to the ballistic amplitude in conjunction with the systolic volume,[14] and changes in this amplitude may be due to changes in either or both, which may reinforce or nullify one another. In going from congestive failure toward a state of cardiac competence, one might expect the effect of an increased stroke volume and improved ventricular con-

traction of the heart to reinforce one another in increasing the ballistic amplitude. Starr[5] observed several cases under treatment with the high-frequency ballistocardiogram, but concluded that the ballistic amplitude could increase or decrease with treatment, and felt that no consistent pattern was recognizable. Mathers, Nickerson, Fleming and Patterson[6] followed 16 patients out of heart failure with the low frequency, critically damped table and concluded that, while abnormality of no specific type was usually present in heart failure, it changed toward the normal in all patients showing clinical improvement. We feel not only that there is a consistent improvement in form of the ballistocardiogram, but a definite pattern of change in the amplitude as well.

In collecting the series of observations before and after therapy, there were excluded from consideration seven patients who had no change or a reduction in amplitude with therapy. All had a common factor of three or more days of hospitalization before the first ballistocardiogram, during which time diuresis, as indicated by daily reduction in body weight, had already been instituted, if not achieved. They also had shown great improvement in such physical findings as had been originally present. This led us to the conclusion that in these cases diuresis was already inaugurated, the maximum ballistic amplitude perhaps reached or passed. This also may explain why the above authors did not find a consistent, though perhaps transient, increase in IJ amplitude with repair of congestive failure.

It is of interest that Starr[5] noted this same temporary increase in ballistic amplitude, and it is manifest in several of the cases presented by Mathers and co-workers,[6] yet neither group attached significance to this finding. Stewart and Cohn,[17] measuring cardiac output by the acetylene technic, found only a transient increase in output despite continued digitalis administration, and La Due and Fahr,[18] using the method of roentgenkymography, concurred in this finding. Studies by Pugh and Wyndham,[19] using cardiac catheterization, indicated that the same unsustained increase in cardiac output occurred with mercurial diuresis. It is perhaps worth mentioning also that most recent studies by cardiac catheterization[20, 21] on the cardiac effects of digitalis were but acute experiments lasting no more than a few hours.

Whether or not the ballistic amplitude or maximum (and minute) stroke force is higher after successful treatment than before, there seems to be a consistent reduction in oxygen consumption with diuresis. The ratio of oxygen consumption to ($F \times P$), which carries the same import as A-V oxygen difference, is most consistently reduced by treatment, and helps explain the apparent return of mechanical forces to pretreatment levels. There is, coincident with the diuresis, which is accompanied by an increased mechanical force, a reduction in pulmonary congestion and dyspnea, accompanied by a reduction in oxygen requirement. Once the demand of diuresis is withdrawn, the mechanical force of the heart at rest falls to the level of activity then required. This may be no higher than the failing heart was able to maintain, yet will be adequate because the output required is less. This situation might also obtain when congestion is minimal and related only to activity, the resting output being equally adequate before and after diuresis. Observations with this admittedly crude instrument indicate no particular difference between the changes induced by digitalis or mercurials except one of timing.

Summary

1. Careful measurement of the time between onset of systole and the occurrence of the I nadir or J peak, as well as the vertical IJ amplitude, is compared between groups of young normals (1), older noncardiac patients (2), patients with clinical arteriosclerotic heart disease (3) and patients with arteriosclerotic heart disease and congestive heart failure, with or without hypertension (4). Serial studies were made in the last group.

2. The incidence of subjects with ballistocardiograms normal in all respects falls with age, is reduced further with disease, and is almost negligible in heart failure. A higher percentage of abnormal tracings is recognized if normal standards for timing of I and J peaks and the IJ amplitude are applied, than if simple notching of various waves is used.

3. In heart failure, a hitherto ignored abnormal H wave, early in systole is present in the majority of cases.

4. The respiratory variation in IJ amplitude was not found to be significantly greater in the patients with arteriosclerotic heart disease than in a group of normals of comparable age.

5. The IJ amplitude, converted to grams of maximum systolic force, was found to increase uniformly after treatment of failure, even though allowance was made for the slight reduction of pulse rate, and especially if related to the reduction in oxygen consumption.

6. Serial studies on patients treated for congestive failure allowed the following conclusions: (a) The transition from congestive heart failure to a state of increased cardiac competence is accompanied by a period of active diuresis, which is uniformly accompanied by a more or less sustained increase in minute systolic force. (b) When originally abnormal, the ballistic form is improved as the amplitude increases. (c) The maximum systolic force is not usually sustained, but falls to an intermediate level, sometimes no higher than the failure level, on compensation; the improvement in form, however, is maintained. (d) Even though minute systolic force is apparently unchanged after the diuresis is completed, this force relative to the oxygen consumption is consistently increased. This is comparable to a decrease in A-V oxygen difference. (e) Failure to respond to digitalis in the above manner is indication that congestive failure was not present.

7. The ballistocardiograph provides a convenient measure of the cardiac activity in and out of heart failure, and, because of the ease of serial observations, can be a useful tool in the evaluation of therapy in congestive failure.

Acknowledgements

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The Ballistocardiogram in Myocardial Infarction: A Study of One Hundred Cases

By MARVIN MOSER, M.D., LEON PORDY, M.D., KENNETH CHESKY, M.D., ROBERT C. TAYMOR, M.D., AND ARTHUR M. MASTER, M.D.

In the presence of previous myocardial infarction, the direct ballistocardiogram is *abnormal* in approximately 80 per cent of the cases. Following the coronary occlusion, a *normal* ballistocardiogram is relatively rare in patients with angina pectoris as compared with those who are asymptomatic. There is no correlation between the ballistocardiographic patterns and the persistence of electrocardiographic evidence of myocardial infarction. The prognostic significance of the ballistic findings reported will be determined by long-term follow-up studies.

SINCE the introduction of a simple direct ballistocardiograph by Dock and Taubman in 1949[1] ballistocardiography has become a clinically feasible procedure which may be carried out in both routine hospital and office practice. Previously, the recording of the movements of the body imparted to it by the force of cardiac action and the movement of blood through the body required expensive equipment with fixed installation and could only be accomplished by workers in large medical centers.[2, 3] Because of this disadvantage the ballistocardiograph was used only for research purposes. The basic work done on these elaborate machines, however, provided important information that can now be applied to the routine study of ballistocardiographic patterns in cardiac patients.

With the newer simple direct ballistocardiographs, the qualitative study of the shapes of the waves and a rough quantitative study of the height and depth of the waves are widely applicable for routine use by practicing physicians.

The use of the ballistocardiogram as an aid in the diagnosis and prognosis of heart disease is now being investigated by many different observers. Reports have appeared confirming the value of the ballistocardiogram in the diagnosis of coronary artery disease[4–8] and congenital heart disease.[9] Several investigators have now followed patients for a sufficiently long period of time to feel that the recording of a normal or abnormal ballistocardiogram is of prognostic significance.[10]

The majority of this reported work has been done on the high frequency undamped table of Starr[2] or the critically damped low frequency table of Nickerson.[3] These instruments record the movements of the body indirectly and are not suitable for use by the practicing physician.

In an attempt to determine the accuracy and value of the photoelectric (displacement) type of ballistocardiograph, the ballistocardiographic records in over 600 patients were studied by directly recording the movements of the body with a modified Dock apparatus. The findings in normal patients[11] and in patients with heart disease[12] have been reported elsewhere. These results have indicated that the records obtained with the simple ballistocardiograph compare favorably with those obtained when more complicated machines are used, and that the ballistocardiogram seems to be of value in the early diagnosis of coronary artery disease. It is the purpose of this paper to describe our findings in 100 patients with previous myocardial infarction.

MATERIAL AND METHOD

We studied 100 consecutive patients who had experienced previous coronary occlusion with myocardial infarction, as confirmed by unequivocal electrocardiographic and clinical evidence at the time of the attack. Seventy-nine were males and 21 were females. Patients with equivocal electrocardiograms or histories were omitted from this group. Patients with previous infarctions but evidence of extensive peripheral vascular disease or hypertension were also excluded from this study because we have

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found that both these entities produce changes in the ballistocardiogram,[12–14] even in the absence of heart disease. Each patient received a routine cardiac study including a 12-lead electrocardiogram and was questioned carefully regarding signs and symptoms which had occurred since the acute attack. Ballistocardiograms were taken at rest in all cases and in a few patients ballistocardiographic tracings were repeated after the "two-step" exercise test.[15] A direct photoelectric ballistocardiograph was used with a ruler or steel bar placed across the patient's shins. This method has been described elsewhere.[11, 16] Tracings were recorded on either a single channel, direct writing electrocardiograph (fig. 1*a*), or on a multichannel machine when pulse tracings or heart sounds were recorded for the timing of abnormal records (fig. 1*c*). Simultaneous electrocardiograms were superimposed on the ballistocardiographic record and were recorded on the single channel machine, when necessary for timing[6, 11] (fig. 1*b*).

The ballistocardiographic apparatus used was devised by one of us (L. P.).[16] The hinges described by Dock[1] are eliminated. The crossbar lies on the patient's shins with the remaining parts free in space; the edge of the crossbar partially occludes light falling on the photoelectric cell below. An Alnico magnet placed within the crossbar serves for recording velocity tracings. Thus, with a single placement of the crossbar, ballistocardiographic records of both the photoelectric (displacement) and electromagnetic (velocity) types may be recorded either simultaneously or successively.

The achievement of standardized recording conditions with this apparatus is effected by connecting a microammeter with the photoelectric cell terminals. The microammeter is utilized in conjunction with a rheostat control knob for standardizing the light output from the photoelectric cell. The crossbar is then placed on the shins between the light source above and the photocell below. Standard setting of the crossbar is then achieved by partially occluding the light and checking the microammeter calibration to a fixed number. The crossbar setting is thus standardized by this technic and records taken repeatedly on the same patient are consistently reproducible.

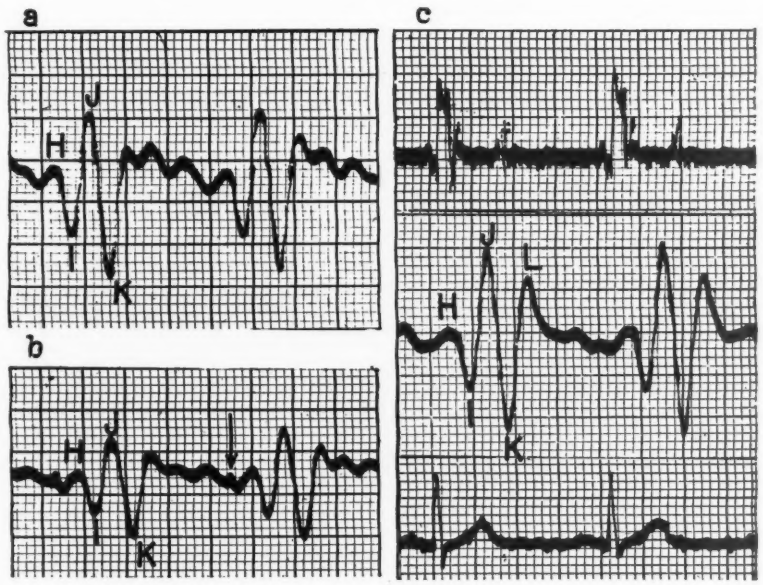

FIG. 1. (*a*) Normal ballistocardiogram. (*b*) Normal ballistocardiogram with simultaneous electrocardiogram. (*c*) Heart sounds, ballistocardiogram and electrocardiogram.

The qualitative appearance of the ballistocardiographic waves was carefully interpreted but no quantitative studies were attempted. A ballistocardiogram was considered normal at rest if it conformed to a pattern similar to that in figure 1 or figure 2, *a* and *b*. If abnormal patterns dominated the tracing, the record was considered abnormal. The occurrence of occasional abnormal complexes was not considered significant as these may represent artefacts. A ballistocardiogram was considered abnormal after exercise if any of the patterns illustrated in figure 2, *c* to *k*, occurred or if the amplitude of the waves failed to increase.

TABLE 1.—*The Ballistocardiogram in Myocardial Infarction*

BCG	Abnormal ECG	Normal ECG
81 Abnormal	74	7
19 Normal	17	2
Total 100	91	9

of 19 patients with normal ballistocardiograms: 17 had abnormal electrocardiograms.

Several types of abnormalities were encountered repeatedly in the 81 patients with abnormal ballistocardiograms (table 2): (A) diminution of the I wave (fig. 2, *e* and *f*), 21 cases; (B) a bizarre pattern with low voltage (fig. 2, *k*),

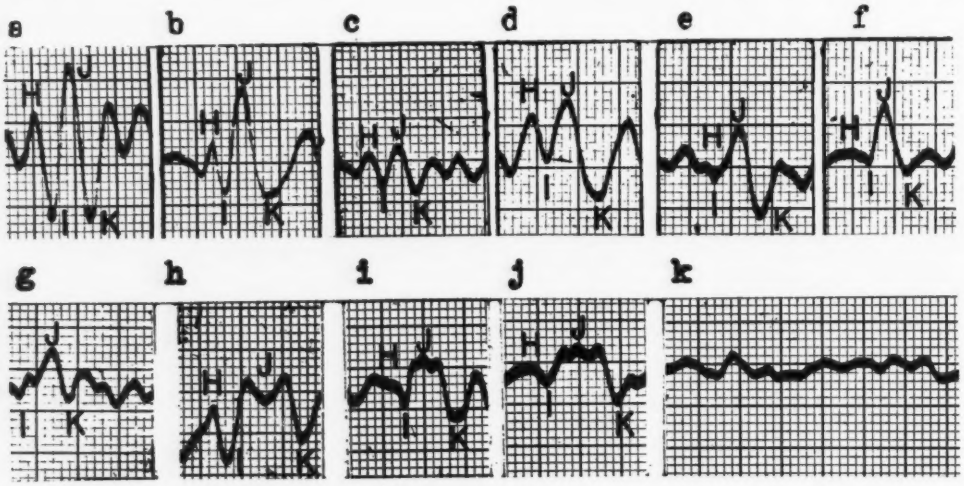

FIG. 2. Variations in the pattern of the ballistocardiogram. (*a*, *b*) Normal patterns, (*c*, *d*) Prominent H wave (early "M" pattern). (*e*, *f*) Small to absent I wave. (*g*) Notched J wave. (*h*) Notched J wave (late "M" pattern). (*i*, *j*) Double and triple notched J wave. (*k*) Bizarre pattern with low amplitude.

TABLE 2.—*Ballistocardiographic Abnormalities in Patients with Myocardial Infarctions*

Pattern	Low I Wave	Bizarre Pattern	Notched J Wave	Prominent H Wave	Low I and Notched J	Low Voltage	Low I Deep K	Total
No.	21	18	15	12	7	6	2	81

All of the abnormal curves encountered in these patients have been described in other pathologic cardiac conditions, and are in no way specifically diagnostic of previous myocardial infarction.

RESULTS

The findings of the ballistocardiograms and electrocardiograms are recorded in table 1. Of the 100 patients who had experienced definitely proved myocardial infarction 3 weeks to 12 years prior to this study, 81 presented abnormal ballistocardiograms at rest while 19 displayed normal tracings. Seventy-four of the 81 patients with abnormal ballistocardiograms showed abnormal electrocardiograms whereas

TABLE 3.—*The Ballistocardiogram and Angina Pectoris Following Myocardial Infarction*

BCG	Angina	Asymptomatic	Average Age
81 Abnormal	26	55	59
19 Normal	2	17	50
Total 100	28	72	

18 cases; (C) a notched J wave (fig. 2, *g*, *h*, *i* and *j*), 15 cases; and (D) a prominent H wave ("early M" pattern of Starr) (fig. 2, *c* and *d*), 12 cases. Other abnormal complexes encountered included the finding of low amplitude

a one in six cases and a low I wave in combination with a notched J wave in seven patients.

Angina pectoris after infarction was noted much more frequently in the patients with abnormal ballistocardiograms than in those with normal ballistocardiographic records. Table 3 lists the relationship between symptomatology (angina) and ballistocardiographic findings following myocardial infarction. However, no correlation appeared to exist between the type of ballistocardiographic abnormality and the severity of the clinical condition of the patient. The average age of the patients with abnormal ballistocardiograms was 59 years; the group with normal tracings averaging 50 years of age.

Discussion

We have examined 100 patients with previous coronary occlusion and have compared their electrocardiograms, clinical histories, and ballistocardiographic tracings. Since the ballistocardiogram and electrocardiogram are records of two different processes, an absolute correlation of these findings is not to be expected and was not obtained. Seventeen of the 19 patients with normal resting ballistocardiograms had abnormal electrocardiograms and seven patients with abnormal ballistocardiograms had normal electrocardiograms.

This lack of correlation is readily explained when one considers the physiologic mechanisms which are responsible for the recording of these tracings. The electrocardiogram reflects the electrical activity of the myocardium, that is, the course of the excitation wave, while the ballistocardiogram is produced as a result of ejection of the blood from the heart.[18] The ballistocardiographic waves reflect the impact and recoil of the body which occurs as a result of the movement of the blood from the heart through the great vessels. Since certain extracardiac factors such as hypertension and peripheral vascular disease produce definite alterations in the vascular system these conditions must be considered in the interpretation of the ballistocardiogram.[12–14] Abnormal tracings may be obtained as a result of these entities and consequently the recording of an abnormal ballistocardiogram in patients with hypertension or peripheral vascular disease does not necessarily indicate an abnormal cardiac action.

A small area of myocardial damage may produce a significant alteration in the electrocardiogram and no alteration in the force of ejection of blood from the heart and thus in the ballistocardiographic pattern. Conversely, a normal electrocardiogram may be obtained in a patient with myocardial damage, but because cardiac function is impaired, the ballistocardiogram may be abnormal. Some young patients who suffer a myocardial infarction secondary to the closure of a small coronary vessel by an atheromatous plaque or secondary to localized "coronary arteritis"[19] probably do not have diffuse coronary artery disease or diffuse myocardial damage. This has been demonstrated pathologically by recent observers.[19] It might be expected that, since most of the myocardium is still intact, these patients would have a normal ballistocardiogram soon after the acute episode and that cardiac function would remain normal. Ballistocardiographic and circulatory studies carried out on the Starr ballistocardiograph[2] have actually demonstrated that the circulatory dynamics and ballistocardiograms of patients with previous coronary occlusion may return to normal within a short time after the occlusion.[7] In these cases, it has been assumed that chronic coronary artery disease is not present. A 25 year old man observed by us probably represents such a case. This patient, who had previously been in excellent health, suffered a posterior wall infarction. He recovered uneventfully, was able to indulge in all activities and had a normal double "two-step" exercise test six months after the coronary occlusion. His ballistocardiogram was normal three weeks after the acute episode and has remained normal both at rest and after exercise. Functional recovery may be assumed since the patient is completely asymptomatic and cardiac function, as judged by the above tests, has returned to normal.[20] In younger persons who suffer myocardial contusions as a result of a laceration or direct injury, functional recovery is also to be expected. In the older group of patients who experience a coronary occlusion it may be assumed that some degree of generalized coronary artery narrow-

ing is present. The degree of narrowing and the extent of the myocardial damage largely determines whether or not these patients will remain symptom-free after their occlusion.

If the patient develops angina pectoris after a myocardial infarction, full functional recovery has apparently not occurred; these patients do not survive for as long a period following the acute occlusion as patients who remain symptom-free.[21] Observers who have had extensive experience with the table ballistocardiograph feel that the tracing obtained may be used as an objective indication of normal or disturbed circulatory dynamics.[7] In patients with angina pectoris following a coronary occlusion the ballistocardiogram may, therefore, serve to substantiate the diagnosis of persistent coronary insufficiency due to chronic coronary artery disease, whereas in patients free of chest pain it may indicate unsuspected abnormalities.

Starr and Hildreth[17] have recently reported on a series of patients whose ballistocardiographic records have been followed for periods up to 10 years following a myocardial infarction. Their results appear to indicate that the prognosis of patients with normal ballistocardiogram following a coronary occlusion is better than that of patients with an abnormal tracing.

Mandelbaum and Mandelbaum[8] also have stated that if the ballistocardiogram is normal or nearly normal following an infarction, the prognosis is better than in those cases with an abnormal tracing. These observers feel that the ballistocardiogram is helpful in evaluating functional recovery of the myocardium. The conclusions reached by these authors, however, were based on short term observations.

Objective evidence to help substantiate the diagnosis of chronic coronary artery disease and angina pectoris was obtained by the use of the ballistocardiogram in 26 of the 28 patients in our series who had symptoms of coronary insufficiency. These patients all showed definitely abnormal ballistocardiographic tracings. In two patients with angina pectoris, the ballistocardiogram was normal. The significance of this finding cannot be stated definitely at present. Whether those patients who have normal ballistocardiograms will survive for longer periods than those with abnormal records can only be determined by careful follow-up studies of these patients as well as other groups of patients who develop symptoms of chronic coronary artery disease following a coronary occlusion.

A normal ballistocardiogram was found in 17 of the 72 patients without angina pectoris. Most of these patients were leading normal lives and none showed any evidence of congestive failure. The remaining 55 patients who were also free of chest pain had abnormal ballistocardiographic tracings. These patients, too, had experienced fairly satisfactory clinical recoveries and did not present significantly different clinical pictures, when compared with the 17 patients with normal ballistocardiograms. The time interval between the occurrence of the myocardial infarction and the recording of the ballistocardiogram was essentially the same in each group of patients. We were unable to draw any definite conclusions regarding the significance of the ballistocardiograms in these cases. If the conclusions of Starr are correct it is to be expected that the prognosis of those patients with normal ballistocardiograms is better than of those with abnormal records despite the fact that at present their clinical status appears to be similar. The real prognostic significance of ballistocardiographic tracings can only be determined by careful long term studies of large groups of patients.

Conclusion

1. The ballistocardiogram is abnormal in approximately 80 per cent of patients with previous myocardial infarction. In approximately 20 per cent of cases it may be normal, regardless of the age of the patient. The ballistocardiogram may remain normal for years following the occlusion.

2. In patients with angina pectoris following a coronary occlusion a *normal* ballistocardiogram is infrequent (7 per cent of cases) when compared with the group of patients with abnormal ballistocardiographic tracings. In these patients the ballistocardiogram may serve as an objective record of the presence of coronary insufficiency.

3. There is no correlation between the ballistocardiographic findings and the persistence of electrocardiographic evidence of myocardial infarction.

4. No definite conclusions regarding the prognostic significance of the direct body ballistocardiogram in patients with myocardial infarction can be drawn until additional careful, long term follow-up studies are done on patients with both normal and abnormal ballistocardiographic records.

ACKNOWLEDGMENT

The authors wish to express their appreciation to Miss Iris Kanner for technical assistance.

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The Ballistocardiogram in a Free Clinic

By JOHNSON MCGUIRE, M.D., GISELA HERWITZ, B.A., AND JOHN R. BRAUNSTEIN, M.D.

Of 240 patients consecutively admitted to the Cardiac Clinic of the Cincinnati General Hospital, and on whom a clinical diagnosis of heart disease was ultimately established, 204 had a ballistocardiogram taken and either an electrocardiogram, a six-foot chest plate or both of the latter two. The ballistocardiogram was evaluated (1) in terms of abnormality of pattern and (2) in degree of deviation from normal initial cardiac force. Frequency of abnormality in the various technics is presented for the group as a whole as well as for several etiologic groups. It is concluded that for a population of this kind the frequency of abnormality in the ballistocardiogram and electrocardiogram is essentially the same, whereas it is somewhat less in the chest plate.

THE electrocardiogram and the chest x-ray are two of the more popular and valuable laboratory aids in the diagnosis of heart disease. The ballistocardiogram is a relative newcomer to the field. The purpose of this paper is to compare the accuracy of the ballistocardiogram in determining the presence of cardiac disorders with that of the other two methods.

Out of 240 patients admitted to the Cardiac Clinic of the Cincinnati General Hospital, 204 had a ballistocardiogram and one, or both, of the other two tests taken. In addition, a clinical diagnosis of heart disease was ultimately established. The electrocardiograms were read in the usual manner and the interpretations classified as normal and abnormal for the purpose of tabulation. The ballistocardiogram was evaluated in terms of the quality of the pattern and the degree of deviation from normal initial cardiac force.[1] Cardiac force was chosen as the quantitative measurement rather than cardiac output since the former can be calculated from any record regardless of the normality of the pattern. Cardiac output calculation, on the other hand, is confined to the normal pattern. The chest x-ray films were read in the usual manner; the transverse diameter of the cardiac silhouette was measured and its normality judged according to the height and weight of the patient. Again, the interpretations were classified as abnormal and normal.

The results of the comparisons are presented for the most part in histograms. This manner of presentation was chosen because the distribution of the measurements upon which the final impressions were based was not normal, for example, that of initial cardiac force was skewed (fig. 1). Under the circumstances, measures of cardiac function would not be expected to have a normal distribution. However, this is approximately normal when cardiac force is calculated from the tracings of a group of individuals without heart disease. For these reasons the more sophisticated statistical methods were not used, since the validity of their results would have been questionable. Instead, all five parameters were divided into normal and abnormal categories and the percentages of abnormality for any particular test calculated and plotted.

Inspection of figure 2 shows that the frequency per cent of abnormal electrocardiograms and ballistocardiographic patterns is within a few points in favor of the latter. When initial cardiac force and the electrocardiogram are compared (fig. 3), it is found that the difference between them is slightly in favor of the electrocardiogram. However, when pattern and force are considered as a unit and compared with the electrocardiogram, abnormality again is more frequent in the ballistic tracing. It should be noted that the ballistocardiogram and electrocardiogram read-

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ings agree in 76 per cent of the cases when ballistic pattern alone is being compared: when it is combined with initial cardiac force the agreement is reduced to 58 per cent.

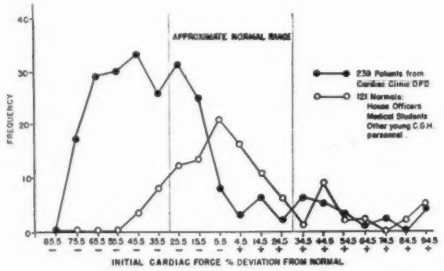
APPROXIMATE NORMAL RANGE
239 Patients from Cardiac Clinic DPE
121 Normals: House Officers Medical Students Other young C.G.H. personnel
FREQUENCY
INITIAL CARDIAC FORCE % DEVIATION FROM NORMAL

FIG. 1. Frequency distribution of per cent deviation from normal initial cardiac force. (From *The Ballistocardiogram* by John R. Braunstein. Courtesy of Charles C Thomas, Springfield, Ill.)

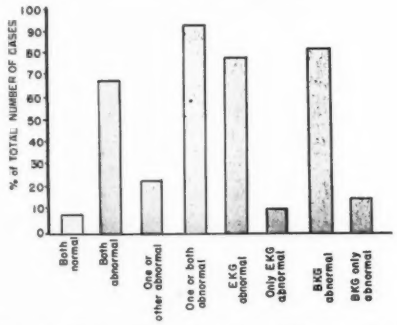

FIG. 2. Frequency of abnormalities in electrocardiogram and ballistocardiogram.

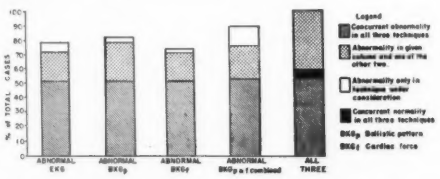

FIG. 3. Frequency of abnormalities in electrocardiogram, ballistic pattern and initial cardiac force. (From *The Ballistocardiogram* by John R. Braunstein. Courtesy of Charles C Thomas, Springfield, Ill.)

Division of the patient group according to diagnosis produces good agreement between results of electrocardiogram and ballistic pattern. In coronary heart disease it is 80 per cent (fig. 4). In hypertensive cardiovascular disease, it amounts to 71 per cent (fig. 5). It is interesting to note here that none of the patients in the first group had normal electrocardiograms and ballistocardiograms simultaneously, but a small number of those with hypertensive cardiovascular disease had. Electrocardiographic abnormality appears about as often as abnormality of ballistocardiogram pattern in coronary heart disease. In patients with hypertensive cardiovascular disease, the ballistocardiogram pattern revealed abnormality somewhat more frequently than the electrocardiogram (10 per cent). An analysis of the findings in the other disease groups is not feasible since the points are distributed too thinly between them.

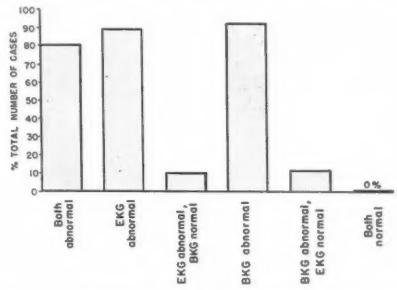

FIG. 4. Frequency of abnormalities of electrocardiogram and ballistocardiographic pattern in coronary heart disease.

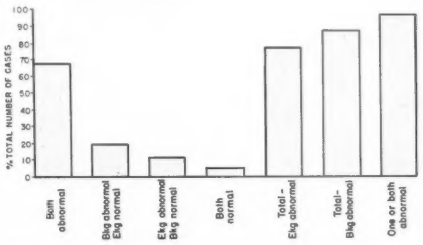

FIG. 5. Frequency of abnormalities in electrocardiogram and ballistocardiographic pattern in hypertensive cardiovascular disease.

When the ballistocardiogram is compared with the x-ray films, it is found that the former shows abnormality more often than the latter (fig. 6), the difference being about 14 per cent. The evaluation of the tests is the same in 79 per cent of the cases. (Evaluation is based on pattern for one and diameter of the heart for the other.) In order to determine if any relationship existed between the initial cardiac

force and cardiac size, the findings recorded by these two means were compared (fig. 7). The results agree in only 56 per cent of the

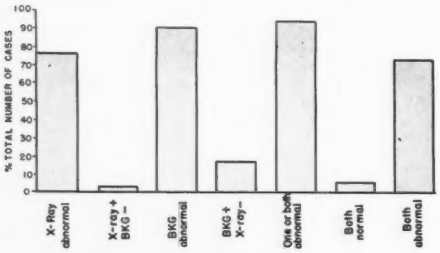

FIG. 6. Frequency of the abnormalities in x-ray and ballistocardiogram diagnoses disregarded.

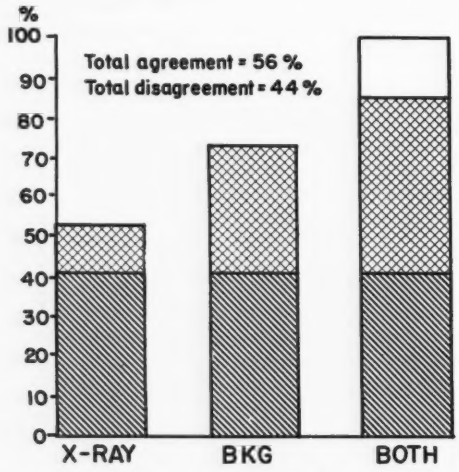

FIG. 7. Frequency of abnormalities in cardiac diameter and initial cardiac force.

cases. Fifty-four per cent of the patients had abnormal x-ray films, but 73 per cent of them had abnormal cardiac force.

Baker, Scarborough, Mason and Singlewald[2] reported in a recent paper that the ballistocardiogram (pattern only) was much more sensitive for detecting abnormality of cardiac function than the electrocardiogram. This is particularly true in early cardiac disease and in angina. Their data are very convincing. The discrepancy between their findings and ours could be explained on the basis of the patient material available and the selection of the cases; Baker and his associates eliminated from their study all those persons who had an enlarged heart on x-ray study and/or systolic blood pressure over 177 mm. Hg. In general, it can be said that the patients examined in the Outpatient Clinic of the Cincinnati General Hospital have fairly advanced cardiac disease, and relatively few are seen whose heart disease is still in the early stages.

Although our data are not as clear-cut as those of the Johns Hopkins group, a slight but consistent trend can be observed. In general, it can be said that for a group of patients like those upon which this study is based, the ballistocardiogram and the electrocardiogram are equally good diagnostic technics. Although they deal with different phases of cardiac physiology, they record abnormality with about equal frequency. The comparison between x-ray findings and ballistocardiogram favors the latter, and is particularly pronounced when cardiac force and transverse diameter are the only criteria used.

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Surgical Treatment of Coarctation of the Aorta in a Ten Week Old Infant: Report of a Case

By John W. Kirklin, M.D., Howard B. Burchell, M.D., David G. Pugh, M.D., Edmund C. Burke, M.D., and Stephen D. Mills, M.D.

Although most patients with coarctation of the aorta survive to early adult life, it has been adequately demonstrated that some patients die in infancy and early childhood as a result of their coarctation. In selected cases, then, operation is advisable at a very early age. Cardiac failure in a 10 week old infant necessitated operation at this age in the case reported.

IT IS our opinion that the optimal age for surgical treatment in cases of coarctation of the aorta is between the ages of about 12 and 20 years; however, if a patient with coarctation of the aorta begins to evidence a complication of coarctation before the age of about 12 years, surgical treatment may have to be undertaken at an earlier age.

Marked cardiac enlargement occurring in an infant or child with coarctation may be regarded as the forerunner of heart failure and is a valid indication for operation as soon as the diagnosis is made, regardless of the age of the patient. Bacterial aortitis may occur at any age in patients with coarctation, although it is less common in coarctation than is subacute bacterial endocarditis on an associated bicuspid valve. Preferably, the bacterial infection should receive adequate treatment prior to consideration of surgical intervention. Should intracranial hemorrhage occur before a patient with coarctation reaches the ideal age for operation, surgical treatment for the malformation is to be recommended 6 to 12 months after the patient has recovered from the acute episode.

Although most patients born with coarctation of the aorta live through infancy and childhood, it is apparent from the experience which is accumulating that death may be caused by the malformation at an extremely early age.[1, 2] The exact mechanism underlying the appearance of left ventricular enlargement, pulmonary congestion and heart failure in the first few weeks of postnatal life in certain individuals with coarctation has not been entirely elucidated. Bahn, Edwards and DuShane[3] have recently reviewed the problem of coarctation of the aorta as a cause of death in infancy and reported three of the cases seen at the Mayo Clinic.

It is mandatory, therefore, that coarctation of the aorta be considered in all cases of otherwise unexplained cardiac enlargement, or cardiac failure, in infancy. This is particularly true, since surgical correction of the malformation is possible even at this early age. Indeed, it is necessary that it be carried out promptly in such cases; else a fatal outcome seems assured. This diagnosis may be suspected when the femoral pulsations cannot be palpated. Accurate evaluation of these pulsations may seem difficult at this age; however, with a little practice, one can acquire skill in detecting femoral pulsations in an infant. The vessel is usually a finger's breadth medial to the anterior superior spine of the ilium. The pulsations can usually be found with ease in the sleeping normal infant by the fifth day after birth. A precise method of determining this malformation exists, namely, aortography, which can be employed in the smallest infant.[4]

It may be mentioned that the main differential diagnoses in such cases are patent ductus arteriosus and endocardial sclerosis of the large ventricle type. When pulmonary edema is prominent, pulmonary venous obstruction such as may occur in anomalies of the pulmonary veins (for example, cor triatriatum) may be considered, but in such cases the left ventricle will not be enlarged.

As an illustration of the feasibility of surgical

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repair of this malformation at an early age, should it prove necessary, a case report is presented.

Report of Case

An 8 weeks old infant was admitted to the Mayo Clinic on March 29, 1951, because of an enlarged heart. The baby, which was delivered by cesarean section, weighed 10 pounds and 2 ounces (about 4.6 Kg.) at birth. The baby cried shortly after birth. Although the baby seemed quite normal during the first few weeks of her life, she began to have some difficulty with her feedings. During the course of the examinations, the physician caring for the baby noted a markedly enlarged heart on roentgenographic examination of the chest.

On admission to the clinic, the baby appeared well developed and well nourished. Development was normal for the child's stated age. Physical examination disclosed no abnormalities save for the cardiovascular system. There was evidence on physical examination of a greatly enlarged heart. No murmurs were heard. Femoral pulsations could not be felt. A roentgenogram of the chest showed the lung fields to be normal. There was, however, evidence of marked cardiac enlargement (fig. 1*a*). The electrocardiogram was consistent with hypertrophy of the right ventricle (fig. 2).

It was believed that coarctation of the aorta was the basic difficulty and the cause of the cardiac enlargement, and aortograms seemed indicated for confirmation. These were taken on April 9, 1951. The left brachial artery was exposed, and a small polyethylene tube was threaded through it into the aorta. The patient was placed on the radiologic table, 5 cc. of 75 per cent solution of sodium iodomethamate (Neo-iopax) were injected rapidly, and two views were taken at one-half second and one second. Then, during the injection of 3 cc. of the same solution two oblique views were taken at one-half second and one second. Following this, the tube was withdrawn and the artery was ligated.

The aortograms (fig. 3*a* and *b*) demonstrated clearly a coarctation of the aorta which was situated just proximal to the origin of the left subclavian artery. There appeared to be some narrowing of the left subclavian artery at its origin. There was no evidence of patent ductus arteriosus. This type o

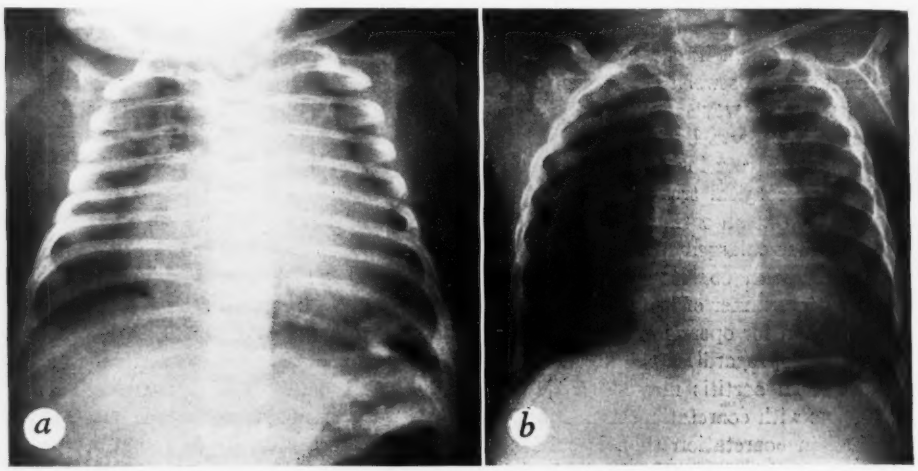

Fig. 1. Roentgenograms of the chest. *a*. Before operation. Note the marked cardiac enlargement. *b*. Seven months after operation.

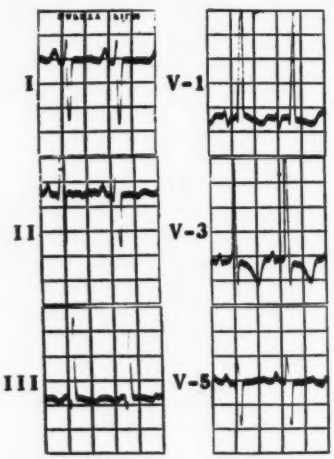

Fig. 2. Electrocardiograms showing findings consistent with hypertrophy of the right ventricle.

coarctation has been recently reviewed by one of us.[5, 6]

Operation was performed on April 13, 1951, at which time the child was 10 weeks old. Anesthesia for the procedure was given by Dr. J. W. Pender of the Section of Anesthesiology, who also supervised the supportive care during operation. The contents of the left thoracic cavity were exposed by a left posterolateral incision, the chest being opened through the fourth intercostal space.

of this structure. The intercostal and internal mammary arteries did not appear enlarged.

All the vessels in the area of the coarctation were carefully mobilized. The ligamentum arteriosum was doubly ligated and divided, as was the left subclavian artery. Clamps were appropriately placed and the coarctated area was excised along with the aortic end of the ligamentum arteriosum and the origin of the left subclavian artery. An end-to-end anastomosis was then effected, utilizing interrupted,

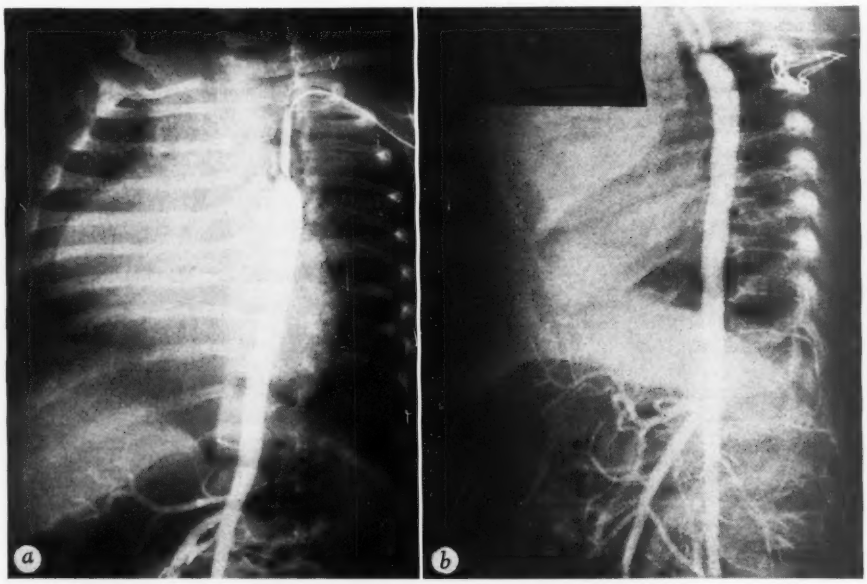

FIG. 3*a* and *b*. Aortograms. Note the constriction of the aorta and slight dilatation of the aorta distal to the constriction.

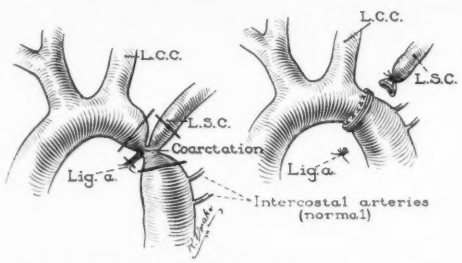

FIG. 4. Coarctation of the aorta in case reported, before and after surgical repair.

The anatomic arrangement of the aortic arch is indicated in figure 4. There was a typical coarctation of the aorta located just proximal to the left subclavian artery. There was a mild narrowing of the left subclavian artery at its origin. The left common carotid artery was normal. The ligamentum arteriosum attached to the aorta just distal to the strictured area and there was no evidence of patency

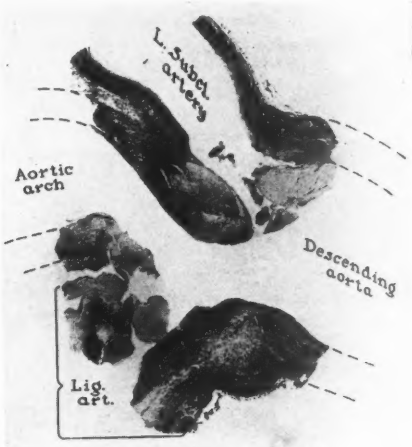

FIG. 5. Retouched photomicrograph of operative specimen.

everting mattress sutures of 5-0 silk. The lumen at the suture line possessed a diameter equal to that of the aorta proximal to it. A retouched photomicrograph of the specimen is shown in figure 5 through the courtesy of Dr. J. E. Edwards.

The baby tolerated the procedure well and the convalescence was uneventful. After the operation, the femoral pulsations were readily palpable. At the time of dismissal, a systolic murmur could be heard over the precordium. This is no longer present. The child's growth and development have been good to date. A roentgenogram of the chest, taken on November 15, approximately seven months after operation, revealed a marked reduction in the size of the heart, relative to the child's size, as contrasted with the preoperative condition (fig. 1*b*).

When the child was re-examined on August 1, 1952, at 18 months of age, the heart was of normal size and the child was developing normally.

Comment

This case emphasizes that coarctation of the aorta may be associated with a serious degree of cardiac enlargement in early infancy. The diagnosis of the malformation by aortography is feasible. A case of successful surgical treatment of the coarctation in such a patient 10 weeks old is reported.

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The Origin of the Variations of Body Impedance Occurring during the Cardiac Cycle

By F. H. Bonjer, M.D., Jw. van den Berg, Ph. D., and M. N. J. Dirken, M.D.

If the trunk is placed between two electrodes of a high frequency circuit, changes in impedance occur during the cardiac cycle. Experiments are presented which show that these variations do not result from the actual volume changes of the heart, as has been suggested in the literature. The changes in impedance are caused by the rhythmic variations in blood content of the vessels.

THE well known fact that a change in volume or in shape of a body placed between two electrodes in a high frequency circuit influences the impedance and may therefore be recorded continuously was used by Atzler and Lehmann,[1] Cremer,[2] Rosa,[3, 4] Holzer and Polzer,[5, 6, 7] Donzelot and Milovanovich[8] in their attempts to study the volume changes of the heart.

In their first publication on this subject Nyboer and his associates[9] also suggested that their "radiocardiogram" is a volume curve of the heart. In later papers, however, Nyboer[10–13] apparently changed his point of view. The spontaneous rhythmic changes in body impedance are regarded as originating solely from the rhythmic fluctuations in caliber of the body vessels caused by the cardiac cycle. For this reason the method is called "impedance plethysmography." The prime importance of the cardiac volume changes has been criticized by Kedrov,[14, 15] Vetter[16] and in a more recent paper by Polzer and Schuhfried.[17, 18] No systematic investigation has, however, been conducted to evaluate both influences which may contribute in the production of the rhythmic variations in body impedance during the cardiac cycle. This has been attempted in the experiments to be reported in the present paper.

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Method

If two electrodes of a high frequency circuit are applied to different parts of the body, fluctuations of the electric impedance during the cardiac cycle may be recorded by the apparatus to be described presently. In the production of these the two above-mentioned factors (changes in the volume of the beating heart itself and the rhythmic fluctuations in caliber of the blood vessels) may play a role. The discrimination between these has been attempted in two different ways. In one series of experiments either the heart or the lung was electrically isolated by putting it in a rubber bag. In model experiments an envelope of this kind had proved to be quite an efficient insulator. The second set of experiments were started shortly after the death of the animal. By inserting cannulas into the aorta and the pulmonary artery (*a*) the heart's ventricles, (*b*) the lesser, and (*c*) the systemic circulation could be connected separately with a mechanical fluid pump. In this way the effect of volume changes of the heart and those resulting from rhythmic perfusion of the blood vessels could be studied separately.

Dogs were used in all experiments. After an initial dose of either morphine (2 mg. per kilogram), Chlorosan (50 mg. per kilogram) and Nembutal (20 mg. per kilogram) or morphine (2 mg. per kilogram), scopolamine (0.2 mg. per kilogram) and Nembutal (30 mg. per kilogram) prolonged anesthesia was obtained by occasional additional injections of Nembutal (10 mg. per kilogram). The animal was tracheotomized and connected with a Starling respiration pump. The spontaneous changes in electrical impedance occurring during the cardiac cycle were recorded during apnea of the animal in order to eliminate the fluctuations caused by breathing. The thorax was opened in the midline by cleaving the sternum; the pericardium was incised and the heart exposed. In order to evaluate the effect of this procedure on the records, the lungs were inflated fully to cover the heart and the chest was temporarily

closed again. Commonly no appreciable differences were noticed between the records taken from the intact dog and after the closure of the thorax. The next step consisted in the electrical isolation of the heart by enclosing it in a rubber bag, which was followed by the wrapping of both lungs in rubber sheeting. At each step a record was made. These were taken after inflation of the lungs, closure of the thorax and during apnea of the animal.

After an intravenous injection of 1.5 cc. of heparin the animal was bled to death from the carotid artery. Immediately thereafter the chest was opened again and both the aorta and the pulmonary artery were transected above the semilunar valves, and brass cannulas were pushed into the ventricles and ligated. The cannulas were both connected with a valveless motor-driven pump, and, by adjusting a screwclamp, the amounts of fluid (gum acacia-saline solution) passing to the ventricles could be equalized. A strong ligature had been placed around the base of the heart across both atria in order to prevent any backflow of fluid. Records were then made in which the pressure in the system was registered by a Statham gage for comparing the impedance changes with the pump cycle.

The chest was now again opened and glass cannulas inserted into the peripherial ends of both the aorta and the pulmonary artery. As the ligature around the atria had been removed and the pump had been provided with a set of valves and connected with a container filled with the gum acacia-saline mixture, the fluid could be driven either through the aorta into the systemic circulation and could leave the body by the right heart and the cannula in the right ventricle or through the pulmonary artery into the lesser circulation and out again by the left heart and the cannula in the left ventricle. On these records, too, both the impedance and the pressure changes resulting from the rhythmic perfusion were registered.

The electrodes (1.5 by 2.5 cm.) were applied to the right foreleg and the left hindleg ("standard derivation") or on each side of the thorax in the axis of the two main branches of the pulmonary artery ("side derivation").

The impedance between a pair of electrodes was measured by a modified Wheatstone bridge which was fed by a generator (14,000 cycles per second). The tissue impedance and a series resistor of 0.5 ohm were placed in one branch and were compared with a fixed impedance in the other branch. Since a change in body impedance affects the balance of the bridge, the bridge voltage may be detected and suitably amplified in one channel of an electrocardiograph. The amplification factor was always kept at the same value. In all records a decrease in impedance corresponds to a rise of the curve. The series resistor of 0.5 ohm could be short-circuited for calibration purposes.

In the experiments on the living animal the electrocardiogram was obtained by the use of a second independent channel of the electrocardiograph after filtering out the high frequency modulation. With the "standard derivation" for the impedance measurement an electrocardiogram was taken from the right and the left foreleg; with the "side derivation" the left side of the chest and the right foreleg were used. In the experiments on the dead animal the second channel recorded the pressure responses of the Statham gage.

Results

In the experiments on the living animal the attempt was made to withdraw either the heart or the pulmonary vascular bed from the flow of electric current between the electrodes by wrapping the heart or the lungs in rubber sheeting. The efficiency of this method had been tested by placing a piece of rubber sheet between two flat electrodes; no current was found to pass. The spontaneous fluctuations in body impedance related to cardiac activity prove not to be influenced at all by wrapping the heart in a rubber bag, at least when the "standard derivation" (right foreleg–left hindleg) is used. The effectiveness of the insulating envelope is obvious from the reduction in size of the ventricular complex of the electrocardiogram. The absence of any notable effect on the impedance record suggests that the volume changes of the vascular bed and not those of the heart are mainly responsible for the spontaneous impedance fluctuations registered from the "standard" leads.

The position of the leads however proves to be very important. If the same experiment is repeated with an electrode placed on each side of the thorax, the curves shown in figures 1 *A* and *B* are obtained.

Since, after the isolation of the heart, the excursions become appreciably greater, it may be concluded that at least under this condition both the volume changes of the heart and the blood content of the vessels play a role. Even under these circumstances, however, when the heart lies between the electrodes, the vascular component prevails. This is clearly shown by comparison of figures 1 *A* and *C*. In the later experiment not the heart but both lungs were wrapped in sheet rubber. The exclusion of the pulmonary vascular bed greatly reduces the

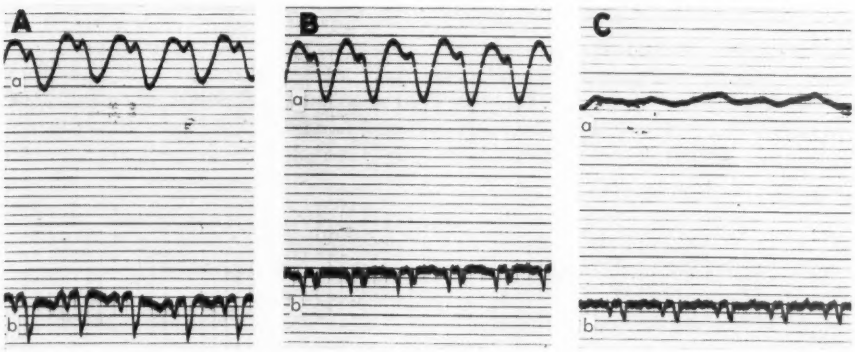

FIG. 1. *A*. Thoracotomized dog: (a) impedance record (both sides of the chest); (b) electrocardiogram (left side of chest-right foreleg).
B. Same dog with heart enveloped in rubber bag.
C. Same dog with lungs wrapped up in rubber sheeting.

excursions of the impedance curve, so that only small atypical fluctuations are left.

In the experiments on the dead animal the effect of artificially induced volume changes of the heart was compared with that of rhythmic perfusion of either the systemic or the lesser circulation. When a valveless mechanical pump is connected with both ventricles and the resistance of the tubes to them is so adjusted that the ventricles receive a nearly equal amount of blood, after closure of the thorax a record is obtained in which the upper curve gives the changes in impedance between the right foreleg and the left hindleg, the lower one those in pressure (figure 2 *A*).

Since in this experiment the stroke volume was maintained at 60 cc. it is plain that pure volume changes of the heart play a very minor role indeed. The experiment was repeated after placing the electrodes at the sides of the chest (fig. 2 *B*). In this situation in which the heart effectively intercepts the flow of the electric current between the electrodes, the influence of the changes in heart volume is well marked.

The perfusion of the systemic circulation and the exclusion of the heart and the lesser circulation was accomplished by connecting the aorta with a mechanical pump provided with valves and by letting the fluid leave the body by the cannula in the right ventricle.

The resulting impedance and pressure records are reproduced in figure 3 *A*. Changing the electrodes from the "standard position" to

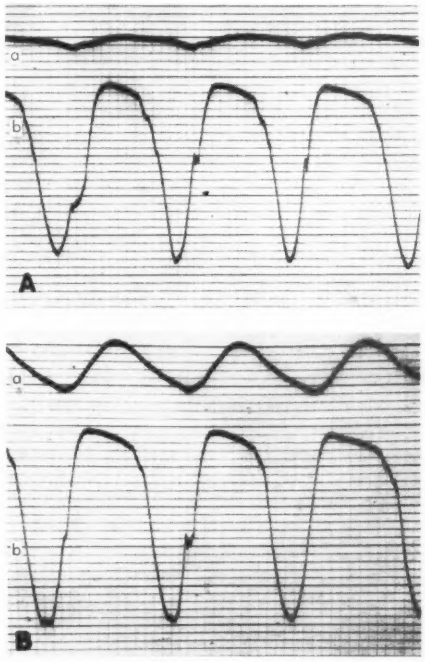

FIG. 2*A*. Artificially induced volume changes of the heart in the dead animal. Stroke volume 60 cc.: (a) impedance record (right foreleg-left hindleg); (b) pressure in ventricles.
B. Same dog: (a) impedance record (both sides of the chest); (b) pressure in ventricles.

the sides of the chest greatly lessens the extent of the excursions, as is shown in figure 3 *B*. This effect strongly indicates that the caliber

changes of the systemic vessels are mainly responsible for the impedance fluctuations shown in the former picture. As the extent of the systemic vascular bed within the chest is relatively small, the "side leads" are only able to pick up small impedance variations (fig. 3 *B*).

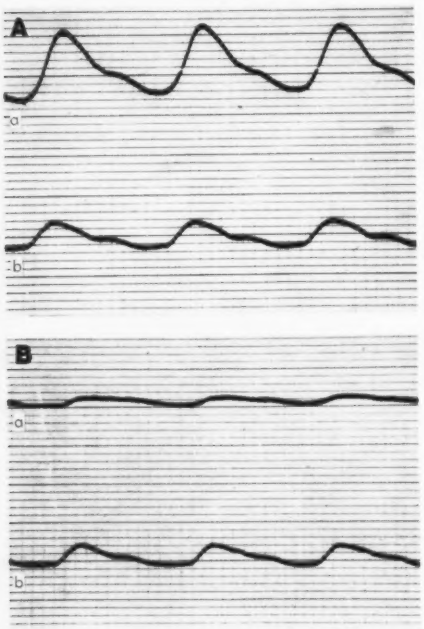

FIG. 3*A*. Perfusion of the systemic circulation in the dead animal. Stroke volume 30 cc.: (a) impedance record (right foreleg–left hindleg); (b) pressure in the aorta.

B. Same animal: (a) impedance record (both sides of the chest); (b) pressure in the aorta.

This being the case, the opposite effect might be expected in those experiments in which only the lesser circulation was perfused. By connecting the outflow tube of the pump with the pulmonary artery and letting the fluid out by a tube in the left ventricle records like those of figures 4 *A* and *B* have been obtained. At the "standard position" of the leads the electric current flows between the right foreleg and the left hindleg and so has to pass the thoracic organs. These, however, only represent a fraction of the total impedance between the electrodes and so the fluctuations caused by the rhythmic perfusion of the lesser circulation are small though well marked (fig. 4 *A*).

A far greater effect results if under identical conditions the electrodes are applied to the sides of the chest (fig. 4 *B*). In this case the rhythmically perfused lungs constitute the major

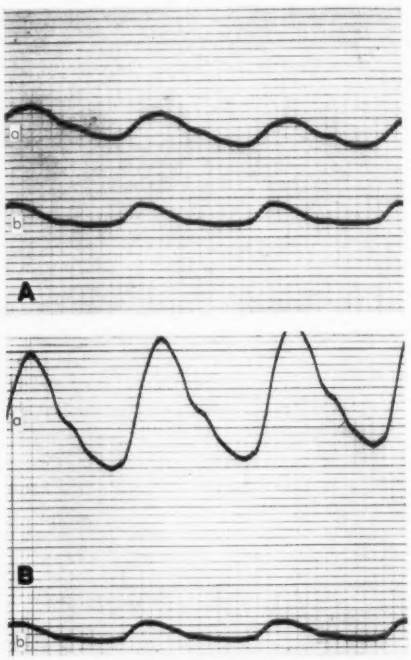

FIG. 4*A*. Perfusion of the lesser circulation in the dead animal. Stroke volume 40 cc.: (a) impedance record (right foreleg–left hindleg); (b) pressure in the pulmonary artery.

B. Same dog: (a) impedance record (both sides of the chest); (b) pressure in the pulmonary artery.

part of the impedance between the leads and the extent of the excursions in figure 4 *B* clearly shows the great influence of plethysmographic changes.

DISCUSSION

The results indicate that the fluid content of the vascular bed between the electrodes is the principle factor in determining the extent of the impedance. The simultaneously registered electrocardiogram and pressure record show that increase in blood content of the tissues goes with increase of current flow and

therefore with decrease of tissue impedance. According to the data on specific tissue impedance of Holzer and of Rajewski as reported by Holzer and Polzer[7] and the slightly different values of Burger and van Milaan,[19] the conclusion seems to be warranted that of all tissues the blood offers the least resistance to the electric current. The replacement of blood by gum acacia-saline solution (0.6 per cent sodium chloride and 6 per cent gum arabic) will have increased the impedance fluctuations recorded in the postmortem experiments by the factor 2, as the specific impedance of the solution amounts to about half that of blood.

Assuming that the blood content of the tissue between the electrodes determines the extent of the recorded impedance fluctuations, we may now attempt an interpretation of the results of those experiments in which the heart beat was imitated by rhythmic pumping of the ventricles. Examples are given in figures 2 *A* and *B*. In the former record "standard leads" were used and so the impedance record fluctuates but little as the change of cardiac volume contributes only a fraction to the total impedance of the tissue between the right foreleg and the left hindleg. The much larger excursions of figure 2 *B* are readily explained by the position of the electrodes. With the leads fastened to the sides of the thorax the heart constitutes an appreciable fraction of the tissue through which the current has to pass, especially in the comparatively narrow-chested dog. For this reason the cardiac volume changes must show up better in the impedance record. In these experiments a rather remarkable phase shift manifests itself as the rise in impedance appears to be retarded with regard to the increase in pressure. In our opinion this phenomenon may be explained by the fact that some head of pressure has to be built up for the dilatation of the ventricular wall and that the inflow of fluid can only occur thereafter. For this reason the start of the ventricular filling is probably more accurately marked by the notch present on the ascending limb of most pressure records instead of by their footpoints.

In the spontaneously beating heart we may also expect that the increase in volume lessens the impedance and so increases the flow of the electric current through the heart. The reverse must occur during systole. As the contraction of the heart tends to increase the impedance but simultaneously decreases it by the expulsion of blood into the vessels of the lesser and systemic circulations, the changes in total impedance must amount to the difference between the cardiac and the vascular factor. This is borne out by comparing figures 1 *A* and *B*. The exclusion of the cardiac factor by wrapping the heart in a rubber bag proves to increase the excursions of the impedance record. As in this instance "side leads" have been used, the volume changes of the heart are mainly compared with the effect of the pulsations of only the pulmonary vascular bed. Even under these favorable conditions the direct influence of the beating heart appears to be very small.

This may sound rather surprising considering that the amount of blood thrown into the lesser circulation cannot be more than about half of the total volume change of the heart during systole. In part the phenomenon may be explained by the physical fact that the decrease in impedance resulting from the inflow of a given amount of fluid depends largely upon the distribution. If this fluid is equally distributed over the electric field between the electrodes, maximum variation will result whereas relatively little change will be seen when the fluid remains accumulated in a small sphere. On the other hand little is known about the spread of the current within the thorax. While it might be argued that with two relatively small electrodes at the sides of the chest the fluctuations in blood content of the whole pulmonary vascular bed must also have been inadequately reproduced, it might have been that in the actual position of the electrodes the cardiac factor was particularly poorly represented in the record.

In order to test this supposition the electrodes were applied to a great number of opposite spots on the chest wall. In the dog no significantly different results were obtained when one or both of the side electrodes were shifted. On the other hand remarkable differences were seen when one electrode was placed on the sternum and the other on the vertebral column.

The interpretation of the resulting curves however was found to be very difficult. It was expected that the shape of the thorax, the situation of the heart near the anterior wall and the absence of a cardiac lobe would make the human subject more suited for studying the impedance changes of the heart. However in most of these cases rather complicated curves were obtained so that a discussion of these had better be postponed.

Summary

The impedance of the body has been described as fluctuating with the beat of the heart. By electrical isolation of the heart or the lungs of the living dog and by artificially induced volume changes of the heart and rhythmic perfusion of the systemic and of the lesser circulation in the dead animal these fluctuations were found principally to result from the expulsion of the blood from the heart during the ventricular contraction. The volume changes of the heart itself generally play a very minor role.

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CLINICAL PROGRESS

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Traumatic Heart Disease
Nonpenetrating Injuries

By R. W. KISSANE, M.D.

IN 1764 Mark Akenside[1] reported the first unquestionable case of myocardial contusion due to a nonpenetrating chest injury. He treated a 14 year old boy who was struck between the ribs by a plate. The boy died six months after the blow; the autopsy revealed an area of necrosis in the left ventricle the size of a half crown extending nearly through the heart wall and covered by adherent pericardium. During almost 200 years, from 1676 to 1868, only 27 cases of traumatic heart disease were reported in the literature.[2] In 1868 Fisher[3] published an impressive description of 76 cases, of which 69 dealt with traumatic rupture and only seven with myocardial contusion. From 1900 to 1937, 108 cases of nonpenetrating injuries to the heart were reported at which time Urbach,[4] in a review of 1000 autopsies of contusion of the chest, found 185 instances of injury to the heart. In 1940 Leinoff[5] reported 50 nonselected consecutive cases of fatal automobile accidents of which eight (16 per cent) showed macroscopic evidence of cardiac damage. In 1936 Glendy and White[6] reported a case of a nonpenetrating wound of the heart, and stated that among 7600 autopsies at the Massachusetts General Hospital not a single case of cardiac trauma of any type was recorded. However, Osborn,[7] in a pathologic study of 202 accidents, found 19 cases of nonpenetrating traumatic lesions of the heart.

Since the year 1930, I have collected 158 autopsied cases of traumatic heart disease due to nonpenetrating injuries. No statement as to general incidence can be made since a large number of these cases or specimens were sent to me because of my interest in the subject. There is nothing to indicate a wide fluctuation in the incidence of myocardial contusion over the centuries, although an increase would be expected with the advent of the automobile and increase in traffic accidents. The reported incidence of traumatic heart disease due to nonpenetrating injuries undoubtedly has been influenced by the general opinion of the medical profession which progressed from considering the condition as impossible or extremely rare to finally accepting it as a possibility in about 15 per cent of all fatal chest injuries.

Experimentally, tears, pericardial and epicardial hemorrhages, were the most frequent injuries produced by blows to the anesthetized dog. They were usually due to moderate blows uncomplicated by myocardial contusion. The anatomic relationship, attachments and structure appear to predispose the pericardium to injury. Similar conditions prevailed in 58 autopsied cases with mild to moderate chest trauma, but with severe, fatal, extracardiac injury; there was subpericardial hemorrhage in 55, pericardial hemorrhage in 21, and small pericardial or epicardial tears in 10. All cases died within three weeks. The subpericardial hemorrhages were usually anterior and varied in size from that of small petechiae to large bruised areas. Subpericardial fibrosis was a frequent finding in a similar group of patients who lived 6 to 18 months after the accident. Uncomplicated hemorrhages of the pericardium and subpericardium, while infrequently found

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at autopsy due to the tendency of patients to recover, probably produce temporary symptoms and electrocardiographic changes.[8]

In the milder instances of trauma the pericardial tears vary from small slits in the visceral pericardium to rents in the pericardial sac. The lesions are generally related to the point of compression against the spinal column due to anterior thoracic trauma. In severe trauma from crushing or falls from heights, the compression force is transmitted more widely and lesions due to bursting may occur some distance from the line of force. There is also a bursting from within due to compression of the great vessels and re-expanding tension of the fluid mass which may rupture the myocardium as well as the pericardium. When cardiac bursting occurs, the wound is invariably larger on the outside with sharp, clean-cut edges, and is lengthwise in the ventricles. Violent displacement of the heart, usually as a result of a fall from high places or other forcible impact, appears to cause tears at the entrance or exit of the great vessels.

Pericardial rupture may be complicated by infection or pneumopericardium due to communication with adjacent injured air containing organs, or by hemopericardium due to myocardial rupture. While herniation of the heart through the torn pericardium is rare, strangulation and sudden death from this cause are observed.

Healing of the minor injuries is usually without adhesion formation. In the more extensive injuries, however, adhesions range from a single fibrous band to adhesive pericarditis with complete obliteration of the sac. Hemorrhage into the posterior mediastinal space frequently is overlooked, but is important because it may cause constriction of the superior vena cava or its branches, the trachea, the bronchi, the nerves in this space, the esophagus, or fixation of the heart in the chest.

There is close similarity between the lesions of myocardial infarction and myocardial contusion.[9] If there is a question of trauma they cannot be differentiated with absolute assurance even by demonstrating an arteriosclerotic lesion at the site of a recent occlusion of a coronary artery, since injury to the vessel wall can also cause thrombosis. Experimental and clinical instances of recent myocardial contusions or injury to vessels are characterized by hemorrhage between the muscle fibers which crowd them aside. A small subendocardial or epicardial hemorrhage is very often the apex of a large triangular area of myocardial contusion. Frequently, fragmentation of the muscle fibers and tears in the papillary muscles are seen. The changes in areas of old hemorrhage produced by severe chest injury are striking. A wall of polymorphonuclear leukocytes intermingled with granules surrounds the area. Muscle fibers partly lose their transverse striations and are swollen with a granular or lumpy protoplasm. These lesions are usually found deep in the fresh specimen and show up very well after fixation. When there is a difference of opinion concerning pathology it is usually in regard to the old lesions. Observation of such healed lesions in dogs and autopsy specimens from persons who had lived six, but not more than 18 months, showed that the muscle fibers which had undergone anemic necrosis were replaced by a gradual absorption by leukocytes and by connective tissue. This led to thinning of the wall and aneurysmal formation.

Subendocardial hemorrhage was found in 90 per cent of the severe, and 50 per cent of the moderate instances of chest trauma. The next most frequent lesion was small endocardial tears with or without tears of the myocardium. The larger hemorrhages had the appearance of a hematoma; sometimes the underlying myocardium was necrotic. The contraction of the scar tissue occasionally causes incompetence of a valve.

Tears due to trauma may occur in normal or diseased valves and great care must be taken to differentiate them from spontaneous rupture. Frequently the tears of a valve cusp do not heal, leaving fragmentation of the free edge and rupture of the chordae tendineae. Healing occurs when the tear is along the base or commissure. However, complete healing with obliteration of the rupture does not occur although the fragments may grow together or become attached to the heart wall. The

tears are only partial because when the rupture occurs, pressure on the cusps is relieved. The passage of a cardiac catheter through a valve against the blood flow frequently will injure or rupture the cusps while passage with the blood stream or retrieving seems to have no effect.

The mitral valve and its large, broad thick cusps supported by chordae tendineae and papillary muscles rather than the cusps, are most frequently ruptured. When the chordae tendineae hold fast, however, the overbending of the cusps during compression of the heart may produce jagged tears in the cusps. Ruptures and tears of tricuspid and pulmonary valves are rare. A traumatized valve is apparently vulnerable to infection which may produce stenosis by the subsequent scarring, thickening, contraction, and adhesion of the cusps. It would be an extraordinary coincidence in which trauma to the heart occurred at exactly the same time that bacteria were in the blood stream; injury to other parts of the body, however, may afford entrance later.

Symptomatology and Diagnosis

More cases of traumatic heart disease are probably overlooked than diagnosed erroneously. The most persistent symptom is precordial pain. The onset may be delayed for six to eight hours. Painful breathing with dyspnea and orthopnea may be observed. Palpitation and tenderness over the precordium are more frequent and may persist for a considerable period of time. The pain of traumatic pericarditis differs from that of myocardial infarction. The latter usually subsides within a short period of time and is accompanied by the clinical picture of coronary occlusion. When a valve is ruptured, the murmur occurs immediately, is loud, constant, and can frequently be heard at a distance from the body. There are also the expected signs of valvular insufficiency. The vibration of a ruptured chordae tendineae produces a sound like a Jew's harp which disappears when the broken ends become entangled or adhere to the side of the heart cavity.

Symptomless myocardial contusions occur but most frequently the characteristic signs are not observed because the patient is unconscious or attention is distracted by severe injuries to other parts of the body. Close questioning frequently discloses that there are two different types of pain present when myocardial contusion is complicated by fractures of the thoracic bony cage. The chief symptom is pain which is identical in character, location and radiation with that of angina pectoris and coronary artery occlusion. There may be a latent period of from a few hours to a few days before the pain develops. Angina of effort frequently develops with dyspnea, and signs of myocardial weakness with congestive failure. All arrhythmias with their characteristic signs and symptoms have been observed. The occurrence of hemopericardium should be suspected if the heart sounds become distant or if, in the presence of shock, the neck veins are distended. Pericardial tap should be done immediately if hemopericardium is suspected. Roentgenographic examination is important not only of the heart but also of the anterior and posterior mediastinal spaces to determine the presence of hemorrhage. Kymoroentgenography and electrokymography offer not only a means of diagnosis, but also a possibility of locating the lesion and its extent.

It may be difficult or even impossible to differentiate myocardial contusion from myocardial infarction because the former with hemorrhage and fragmentation and the latter with myomalacia produce the same signs and symptoms. Much depends upon a careful history. These considerations also apply to angina pectoris; every effort should be made to ascertain the condition of the heart prior to the injury. There is always the possibility of the coincidental occurrence of coronary artery occlusion but too many cases of chest injury have been followed by this condition to call them all coincidental. It is also well to remember that contusion can occur to a heart already damaged by disease or arterial damage.

Almost every arrhythmia has been produced experimentally by nonpenetrating chest injury. The location of the contusion influences the type of arrhythmia with its characteristic signs, symptoms, and electrocardiographic changes. Myocardial, pericardial, and endo-

cardial injury produce changes in the RS-T component and T waves similar to those produced by disease, and may be identical with those of coronary artery occlusion. The unipolar leads are useful in locating the position of the injury.

Cardiac rupture is accompanied by pain and sudden collapse. As the circulation fails, marked pallor, cyanosis, and finally unconsciousness develop. The pulse and heart rate may be slow at first but as tamponade develops the pulse becomes very rapid and weak. The heart sounds are distant and muffled. The arterial pressure falls and the venous pressure rises. There is an increase in the area of cardiac dullness on percussion and of the cardiac silhouette on roentgenographic examination. Pericardial tap and withdrawal of blood is a definite aid in establishing the diagnosis; however, tears of pericardial vessels may also cause hemopericardium. Rupture of the cardiac septum occasionally occurs as the result of necrosis.

Management and Treatment

The general program of treatment of myocardial contusion is similar to that of coronary artery occlusion. The period of bed rest should be from two to four weeks. Patients with severe myocardial contusion should be given oxygen continuously for the first four to seven days to alleviate pain, dyspnea, orthopnea and cyanosis. The anginal pain is not affected by any of the coronary vasodilators. The anxiety usually requires a sedative or narcotic. Digitalis is of benefit in auricular fibrillation and congestive failure but does not control the usual tachycardia. Digitalis should not be used routinely because it increases the frequency of ectopic rhythms, suggesting that the irritability of damaged myocardium is increased by digitalis.

The arrhythmias have a tendency to revert spontaneously to normal rhythm, but auricular fibrillation frequently is persistent and requires quinidine therapy. It is advisable to give Pronestyl or quinidine for the first few days for prevention of the more serious cardiac irregularities. When pulmonary edema occurs it should be treated by the usual accepted methods; venesection is not advisable because pulmonary edema is almost invariably the result of pulmonary trauma.

Many patients with serious cardiac injuries arrive at the hospital unconscious and in extremis, but the possibility of survival should not be doubted. Beck[10] has advised repeated pericardial tapping in cases with tears and rupture in order to relieve cardiac tamponade until operation can be performed. If cardiac standstill occurs, the heart should not be massaged because of the danger of increasing the area of contusion and hemorrhage. Although massage is frequently successful, the results are usually only temporary; it is safer to use electrical stimulation or intracardiac injection. Occasionally adhesions, the result of hemorrhage, or a decrease in the anterior-posterior chest diameter from fractures of the bony cage, require surgical correction.

Prognosis

Myocardial contusions tend to heal when they are not multiple or extensive and when only one layer of the heart wall is involved. Immediate death does not always occur even from cardiac rupture, especially when located in the septum. Sudden fatal arrhythmias have been produced experimentally in dogs by nonpenetrating chest injury in the absence of cardiac pathologic changes at autopsy. This emphasizes the importance of injuries which involve the intrinsic nervous mechanism of the heart. Anderson[11] summarized the possibilities following myocardial contusion as complete recovery, reduced cardiac capacity, pain on effort, and congestive failure or rupture. Slight epicardial injuries heal more readily than those of the endocardium probably because blood does not enter the tear and cause dissection. Extensive pericardial lesions may produce adhesions, obliterate the pericardial sac and result in myocardial insufficiency and failure. As with complete rupture, cardiac tamponade can result from pericardial tears and hemorrhage. The clot formation in the sac may embarrass the heart or the blood may escape into the pleural cavity.

Small endocardial lesions, in spite of the possibility of dissection and mural clot forma-

tion, usually recover completely. The possibility of emboli is always present. Valvular rupture is not associated with sudden death but results in permanent damage. The duration of life is short following rupture of the aortic valve because of the difficulty of the left ventricle to compensate for sudden aortic insufficiency. Rupture of the mitral and other valves causes cardiac hypertrophy and predisposes to congestive failure.

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ABSTRACTS

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BLOOD COAGULATION

Perlick, E., and Schmidt, G.: Angioorganopathies and the So-called Prothrombin Utilization Test. Ztschr. Kreislaufforsch. **40**: 690 (Nov.), 1951.

The authors describe a modification of Quick's prothrombin test, which may be used for evaluation of the various accelerator factors in the blood serum. The principal modification consists in the use of pure fibrinogen instead of prothrombin-free plasma so that the reaction becomes dependent on factors present only in the examined plasma solution. The reaction is followed within the first hour instead of the usual determinations at hourly intervals.

This "prothrombin utilization test" was performed on 50 patients with peripheral arterial or venous angiopathies. Compared with normal values obtained in 25 healthy persons, the prothrombin time was increased in 29 out of 42 cases with disturbance of the peripheral arterial circulation. When the cases were divided into two age groups, the test was positive (elevated) in 76 per cent of patients less than 55 years of age. Of eight patients with abnormalities of the peripheral venous circulation, seven had abnormally elevated prothrombin times. The results were independent of concomitant alterations of the erythrocyte sedimentation rate.

PICK

Cole, F., and Kleitsch, W. P.: Incompatibility of Lumbar Block and Anticoagulant Therapy. J. A. M. A. **147**: 1233 (Nov. 24), 1951.

Paravertebral procaine injections are usually considered to be completely innocuous. Complications following these injections are exceedingly rare in normal patients; however, deep injection of procaine in a hypocoagulatory patient (who has received heparin or dicumarol) may be followed by serious effects.

The authors suggest that in phlebothrombosis anticoagulant therapy without paravertebral block be used. Thrombophlebitis requires a lumbar block more urgently than it does anticoagulant therapy. In frostbite or impending arteriosclerotic gangrene when both anticoagulants and lumbar blocks are indicated, it would be wiser to do lumbar sympathectomy and follow this by anticoagulant therapy in the postoperative period.

The authors report the case of a 54 year old white man who was given a lumbar sympathetic block after a course of bishydroxycoumarin. Four days later the patient became sick and on the following day there was evidence of a mass in the right lower quadrant. Evacuation of blood from the psoas muscle was done and the contents of an ampule of topical thrombin were irrigated through the psoas muscle fibers. No evidence of a bleeding vessel was found during the surgical exploration. The use of bishydroxycoumarin was discontinued.

KITCHELL

Gripe, R. H.: Severe Hemorrhage due to Tromexan. New England J. Med. **245**: 803 (Nov. 22), 1951.

One death and two nearly fatal hemorrhages following the use of Tromexan are reported. The death occurred in a patient with rheumatic heart disease, auricular fibrillation and multiple emboli and was attributed to gross hematuria and a subarachnoid hemorrhage.

The drug was administered in doses designed to maintain the prothrombin time between 30 and 50 seconds, but hemorrhage occurred when the prothrombin time rose abruptly to levels between 140

and 360 seconds. Consideration of the prothrombin time of the current day alone is not sufficient basis on which to determine dosage. The general trend of the prothrombin curve must also be considered. Additional anticoagulant is needed in the presence of a falling curve to maintain a therapeutic level, and less is required when a rising curve is present.

Tromexan possesses an extra margin of safety over dicumarol because of rapid absorption and excretion, but it can cause hemorrhage, particularly in patients who are seriously ill. The same precautions must be observed with Tromexan as are customarily in use with dicumarol.

ROSENBAUM

Cadenhead, R. M., and Aberd, M. B.: Pulmonary Embolism after Treatment with Heparin. Lancet. **261:** 865 (Nov. 10), 1951.

A patient suffered a pulmonary embolism 11 days after the end of his first course of heparin for the treatment of superficial thrombophlebitis. The authors feel that this embolism was probably due to direct extension of the thrombus to the deep veins of the leg or buttock with subsequent fragmentation of the clot.

The possibility is briefly mentioned that the initial heparin may have upset the physiologic control of this blood clotting mechanism so that when the heparin was discontinued there was a back swing toward excessive clotting.

TANDOWSKY

CONGENITAL ANOMALIES

Berthrong, M., and Sabiston, D. C., Jr.: Cerebral Lesions in Congenital Heart Disease. Bull. Johns Hopkins Hosp. **89:** 384 (Nov.), 1951.

A study was made of 162 autopsies of patients with congenital heart disease, 135 of the cyanotic type and 27 of the acyanotic type.

Cerebral infarctions were found in 25 of the 135 autopsies on patients with cyanotic heart disease. Both arterial and venous thrombosis occurred. There were 62 cases of tetralogy of Fallot, of which 13 had cerebral infarctions. These did not show any greater increase in the degree of polycythemia than did the 49 cases without lesions. However, it is emphasized in cases with polycythemia, that any state which leads to increased polycythemia, to endothelial damage or to decreased blood flow may result in prompt intravascular thrombosis. Several mechanisms may have been responsible for the cerebral thrombosis: peripheral venous thrombosis which reaches the cerebral arteries as paradoxic emboli through cardiac defects, the development of thrombosis in situ in the cerebral arteries or embolization to the brain from mural thrombi in the cardiac chambers. An increase in hemorrhagic infarctions in the immediate postoperative period may have been due to an increase in platelet formation, shock, and hemoconcentration. Brain abscesses occurred in five patients, suggesting a greater frequency in cyanotic congenital heart disease.

In the 29 patients of the acyanotic group, cerebral lesions were present, but were usually not thrombotic in nature. Ten of these patients had coarctation of the aorta; four had aneurysms of the circle of Willis; three of the four died of a massive subarachnoid hemorrhage. There was one patient with a surgically cured patent ductus arteriosus who also died of a hemorrhage secondary to a ruptured congenital aneurysm of the circle of Willis. One patient had a brain abscess secondary to an osteomyelitis.

MARGOLIES

Clay, R. C., Elliot, S. R., II, and Scott, H. W., Jr.: Changes in Blood Volume Following Operation for Pulmonic Stenosis: Studies with Evans Blue and Radioactive Phosphorus. Bull. Johns Hopkins Hosp. **89:** 377 (Nov.), 1951.

In 10 patients with pulmonic stenosis and a right to left intracardiac shunt, the authors determined the plasma volume by the Evans Blue dye method, the blood volume by the radioactive phosphorus technic and the red cell volume by the difference between these two values. None of the patients was in cardiac failure at the time of testing. The results showed a diminished plasma volume, an increased red cell volume and an increased whole blood volume when compared with normal convalescent individuals.

An anastomosis was later established between a systemic artery and a pulmonary artery. Plasma volume and whole blood volume were measured from 3½ to 13 months following operation. Nine of the 10 patients were greatly improved by the operation, showing an increase in plasma volume ranging from 49 to 1394 ml., a fall in the peripheral hematocrit from 5.6 to 31.0 per cent and a decrease in the red cell volume from 269 to 3430 ml. One showed little improvement, with a drop in plasma volume by 80 ml. and a fall in hematocrit of less than 1 per cent. Eight patients showed a decrease in whole blood volume ranging from 220 to 2920 ml; two markedly benefited by operation, the whole blood volume being greatly increased.

The authors state that after an adequate pulmonary blood flow has been established by operation, there is, in addition to a great reduction in red cell volume, a rise in plasma volume with the result that whole blood volume, although somewhat reduced, still remains moderately elevated above the normal values.

MARGOLIES

Andersson, T.: Electrokymographic Studies in Pulmonary Stenosis and Tetralogy of Fallot. Acta Radiol. **36:** 345 (Nov.), 1951.

The authors describe the electrokymographic findings in four cases of pure pulmonary stenosis,

in one case of pulmonary stenosis with auricular septal defect, in three cases of tetralogy, and in one case of auricular septal defect and hypoplasia of the pulmonary artery. In general, the curves showed a gradual ascent in the period of ejection in contrast to the normal steep rise; a sort of plateau in these cases instead of the descent and incisura of normal pulmonic valvular closure; one case even had an anacrotic notch.

In the discussion the author believes that a distinction may be made between the infundibular and valvular types of stenosis, on the basis of a preliminary ascent of relatively normal grade but of brief duration in valvular stenosis; absence of this ascent in infundibular stenosis is distinctive.

SCHWEDEL

CONGESTIVE HEART FAILURE

Emerson, K., Kahn S. S., Vester, J. W. and Nelson K. D.: Oral Use of Cation-Exchange Resins in Treatment of Edema. Arch. Int. Med. **88:** 605 (Nov.), 1951.

The oral administration of cation-exchange resins for the removal of sodium from the intestinal tract in patients with edema has been investigated and found to be a practical and useful procedure. The amount of sodium removed is variable, ranging from 0.25 to 0.8 mEq. per gram of resin, sometimes reaching higher levels for short periods. The total quantity removed is only partly dependent on the sodium ingested, and it is possible to remove sodium from body fluids and thereby to achieve a negative sodium balance. For practical purposes a daily dose of 45 Gm. may be expected to remove approximately 2 Gm. of sodium chloride, although the figure will vary considerably above and below this level in individual patients. Larger doses may be given but are likely to be poorly tolerated because of their bulk.

Since most resins remove more potassium than sodium, at least 1.3 mEq. of potassium (equivalent to 0.1 Gm. of potassium chloride) must be supplied per gram of resin administered. This may be incorporated in the resin itself. It is probably also advisable to give small amounts of extra calcium. Resin therapy should not be employed in patients with significant degrees of renal insufficiency. The loss of base in the feces must be compensated for by renal ammonia and acid production, or systemic acidosis will result.

BERNSTEIN

Goldman, R.: Studies in Diurnal Variation of Water and Electrolyte Excretion: Nocturnal Diuresis of Water and Sodium in Congestive Heart Failure and Cirrhosis of the Liver. J. Clin. Investigation **30:** 1191 (Nov.), 1951.

The excretion of water, sodium and potassium was studied in eight patients with heart disease, 13 with cirrhosis of the liver, and eight with normal renal and cardiac function. Food and fluid was administered in the usual way. The control group had a minimal output of water sodium and potassium from midnight to 8:00 a.m., with a gradual rise to a maximum between noon and 4:00 p.m., followed by a slight decline to midnight. Similar findings were noted in two of the eight patients with compensated congestive heart disease. In six, however, there was a marked alteration of a pattern with nocturia, with a maximum output of water and sodium between midnight and 8:00 a.m. and the minimum between 8:00 a.m. and 4:00 p.m. Potassium output was erratic. In this group there was no constant relationship between the output of creatinine and any of the other values determined. The reversal of the normal day/night ratio for excretion of water and sodium was more consistent in the patients with cirrhosis of the liver.

The usual cardiorenal hemodynamic explanation for the nocturnal diuresis of sodium and water in congestive failure does not satisfactorily explain the similar nocturnal diuresis in hepatic cirrhosis. It is possible that the nocturnal diuresis may be the result of alterations in tubular functions, mediated by a humoral agent that can be affected by the liver.

WAIFE

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Miller, R. D., Burchell, H. B. and Edwards, J. E.: Myocardial Infarction with and without Acute Coronary Occlusion. Arch. Int. Med. **88:** 597 (Nov.), 1951.

A study of 143 cases of fatal acute myocardial infarction was made to determine the influence of cardiac hypertrophy on the production of acute infarction in the absence of acute coronary occlusion. In 49 cases in which no recent coronary occlusion was observed, the average cardiac hypertrophy was 70 per cent above normal. Approximately three-fourths of the hearts in the group showed hypertrophy of at least 50 per cent above normal. In contrast, in the 94 cases in which there was acute coronary occlusion the hearts averaged 50 per cent over their normal predicted weight. Less than half the hearts in the latter group showed hypertrophy of at least 50 per cent above normal.

Coronary sclerosis in the two groups appeared of equal severity. The anterior descending coronary artery in each group showed the greatest degree of narrowing. The incidence of antecedent hypertension, cardiac failure, and old infarction, all considered to be factors leading to cardiac hypertrophy, was greater in patients with "coronary insufficiency" than in those with acute coronary occlusion. In hearts in which no recent coronary occlusion was found, the infarct was most frequently subendocardial in distribution, and in this group

there was a low incidence of cardiac rupture and pericarditis. With acute coronary occlusion, the infarct was usually transmural and there was a much higher incidence of cardiac rupture and pericarditis as compared with the group with myocardial infarction but without acute coronary occlusion. Thromboembolic complications occurred with equal frequency in the two groups.

BERNSTEIN

Stein, I., and Wroblewski, F.: Myocardial Infarction in Wolff-Parkinson-White Syndrome. Am. Heart J. **42:** 624 (Oct.), 1951.

The authors present a case report where the electrocardiogram was diagnostic of infarction in the presence of anomalous atrioventricular conduction (short P-R interval and prolonged QRS). The patient, a 56 year old woman, presented a typical clinical picture of myocardial infarction. An electrocardiogram on the second hospital day showed a shortened P-R interval, prolonged QRS complex, and T waves deeply and symmetrically inverted in precordial leads. Two weeks later normal conduction occurred, revealing a pattern of anterolateral myocardial infarction. This case is unique in that the spontaneous appearance of normal conduction confirmed the clinical suspicion of acute myocardial infarction. Frequent serial tracings should be obtained in similar cases with the hope that spontaneous appearance of normal conduction may be manifest.

HELLERSTEIN

Connolly, E. P., and Littmann, D.: Coronary Arteriosclerosis and Myocardial Hypertrophy. New England J. Med. **245:** 753 (Nov. 15), 1951.

A study of the weight of the hearts was made in 51 patients with extensive coronary artery disease. Thirty patients had no history of hypertension and no pathologic changes to suggest its presence; cardiac hypertrophy was present in 28 and the evidence suggested that, in general, the more extensive the coronary involvement the greater the hypertrophy. The heart-weight to body-weight ratio averaged 0.64 per cent in these patients in contrast to a normal value of 0.50 per cent.

There were 21 patients with coronary artery disease and hypertension. The average heart weight in this group was one-third greater than in those without hypertension, and the heart-weight to body-weight ratio averaged 0.79 per cent. When congestive heart failure was present in the patients without hypertension, the heart was definitely heavier than when it was absent.

The authors express the belief that cardiac hypertrophy occurs in coronary artery disease as a result of myocardial injury, due to coronary inadequacy, which leads to impaired nutrition of muscle fibers. Furthermore, this injury occurs at those times when the demands on the myocardium exceed the available coronary supply. In the intervals between these excessive demands, the coronary supply is not only sufficient to meet metabolic needs but is even adequate to permit the development of additional muscle tissue.

ROSENBAUM

Baer, S., Heine, W. I., Krasnoff, S. O.: The Mortality of Acute Myocardial Infarction in Private Practice. Am. J. M. Sc. **222:** 500 (Nov.), 1951.

Representative published studies on the immediate mortality of acute myocardial infarction have indicated death rates varying from 80 per cent to 51 per cent, the majority being in the neighborhood of 20 to 35 per cent. The authors, however, from their experience with patients seen at home, questioned whether the prognosis of acute myocardial infarction was as poor as it seemed from hospital statistics and published mortality studies.

To that end, they reviewed 3200 electrocardiograms taken in private practice, and selected 182 cases that met rigid electrocardiographic criteria for the diagnosis of acute myocardial infarction. The age incidence, sex ratio and localization of the infarctions corresponded closely to the distribution of these factors in 1220 cases previously studied in one hospital. The mortality rate in these 182 cases, treated at home by 67 physicians, was 8.5 per cent. Only 4 per cent received dicumarol.

From these findings, it would seem that studies of the mortality of acute myocardial infarction, based on hospital data alone, are unduly and incorrectly biased. The advisability of routinely hospitalizing all patients with acute myocardial infarction seems questionable. Some doubt is also cast on the necessity of administering dicumarol to every case of acute myocardial infarction. Furthermore, the authors feel that the ominous prognosis usually associated with acute myocardial infarction is unjustified.

SHUMAN

ELECTROCARDIOGRAPHY

Mahaim, I., and Suriyong, R.: A New Instance of "Double Cannon" According to Duchosal in a Case of Atypical Right Bundle Branch Block Associated with Atrio-ventricular Block. Cardiologia **19:** 70 (Fasc. 1), 1951.

The authors present phonocardiographic observations in a case of complete A-V block and an idioventricular pacemaker with the pattern of right bundle branch block. The first heart sound was reduplicated and its two components showed marked and independent variations of intensity. Both were faint when the P-R distance in simultaneous recorded electrocardiograms was more than 0.18 second, or less than 0.04 second. P-R distances between 0.11 and 0.14 second produced a loud first component while P-R distances of 0.04 to 0.08 sec-

ond increased the loudness of the second one. The phenomenon is ascribed to the interplay of two factors.

Asynchronous ventricular contraction, due to the conduction delay in one ventricle, leads to dissociation of the closure of the A-V valves and, thus, to splitting of the first heart sound. Since the loudness of the latter depends on the position of the valves at the time of their closure, the intensity of each of the two components changes with variations of the time interval, which separates auricular contraction from the contraction of the right or left ventricle respectively.

PICK

Lasser, R. P., and Grishman, A.: Spatial Vectorcardiography: Right Bundle Branch Block. VIII. Am. Heart J. **42:** 513 (Oct.), 1951.

The authors describe the vectorcardiographic changes which were observed in one patient with transient atypical right bundle branch block, present the variety of spatial forms and orientations recorded, and observations upon the effect of right bundle branch block on the spatial vectorcardiograms of patients with disease states.

"Classic" right bundle branch block is associated with a QRS S_E loop inscribed in the right, lower, anterior octant. The progress of the wave of accession is slow, and the time markers are closely spaced throughout the QRS S_E loop. The QRS loop is open, forming a positive S-T vector which is directed upward, posterior and to the left, producing S-T elevation in aV_R and aV_L, with S-T depression in the foot lead. The T S_E loop points upward, backward and to the left. This pattern appears like the mirror image of what has been observed in left bundle branch block.

Atypical (or Wilson) right bundle branch block is characterized by alteration chiefly of the terminal portion of the QRS S_E loop. This terminal portion is increased in duration, slow and irregular in contour, and invariably directed to the right and anteriorly. This produces the broad S wave of lead I, and the R′ or late R wave of V_1. The T loop axis is directed opposite to that of the terminal portion of the loop rather than opposite to that of the axis of major portion of the ventricular loop. In the patient with transient right bundle branch block, the T S_E loop increased in size and shifted more than 100 degrees, being directed to the left and posteriorly. The T waves in V_1 and V_2 changed from upright to inverted. In patients with left ventricular hypertrophy and right bundle branch block, the failure to find inverted T waves in leads I and V_5 or V_6 is accounted for by the obscuring effect of right bundle block on the T wave and loop. The presence of myocardial damage, myocardial infarction, and left ventricular hypertrophy could be determined from the configuration of the QRS S_E loop alone.

HELLERSTEIN

Levine, H. D., and Phillips, E.: An Appraisal of the Newer Electrocardiography: Correlations in One Hundred and Fifty Consecutive Autopsied Cases. New England J. Med. **245:** 833 (Nov. 29), 1951.

A correlation of electrocardiographic and pathologic studies was made in 150 consecutive patients. The electrocardiographic studies consisted of at least one complete set of conventional standard and unipolar extremity and precordial leads. A high degree of accuracy was demonstrated in the diagnosis of uncomplicated acute myocardial infarction, uncomplicated left or right ventricular hypertrophy or acute cor pulmonale.

The diagnosis of old myocardial infarcts or multiple myocardial infarcts was quite inaccurate. When also present, left ventricular hypertrophy often masked the changes of right ventricular hypertrophy or myocardial infarction. However, the electrocardiograms were not normal in any case of acute or old myocardial infarction. Abnormal but nonspecific electrocardiograms, usually showing abnormalities in the T waves or low voltage, were recorded in a wide variety of pathologic conditions but normal electrocardiograms generally signified normal hearts.

It is concluded that the most important contribution of the newer methods of electrocardiography has been to provide a rational rather than empiric approach to the subject, making possible a better understanding of the electrocardiogram.

ROSENBAUM

V. Luterotti, H.: How Far Are Wilson's Viewpoints in Agreement with the Vector Analysis of the Electrocardiogram? Ztschr. Kreislaufforsch. **40:** 672 (Nov.), 1951.

There are two explanations of the genesis of Wilson's system of "unipolar" leads. According to one school, the various leads represent partial potentials derived from limited areas of the cardiac surface. According to the other explanation, which is based on vectorial analysis, these leads are projections upon various planes of integrated potentials developed in the entire heart.

Actually these two viewpoints are not in complete disagreement. Thus, Wilson's explanation of the typical qR pattern in left and rS pattern in right precordial leads implies the concept of changing direction of instantaneous vectors during the process of ventricular activation. However, while left precordial leads are true reflections of the electrical events at the apex and, therefore, in the left ventricle, right precordial leads cannot simply be identified as right ventricular potentials, since the elec-

trode in the latter position actually faces the right auricle. The term "potentials from the right side of the septum" seems more adequate for the usual pattern of V_1 and V_2.

The "electrical position," defined in normal hearts, by the appearance of "right and left ventricular patterns" in the various leads, is frequently in agreement with the anatomic position of the heart and, therefore, also with the direction of its main vector. This, however, is not true in cases with abnormal ventricular activation as in bundle branch block or in the presence of myocardial infarction. The development of deep Q waves in the latter instances is better explained by disturbance of the normal balance of potentials developed in opposite ventricular walls than by the assumption of a "window effect" in the infarcted area.

"Unipolar" extremity leads do not essentially differ from standard leads, since both are derived from the same (frontal) plane. They are useful in the recognition of cardiac hypertrophy and of myocardial infarction by increasing the number of "points of observation" and thus amplifying diagnostic possibilities. Unipolar leads cannot replace the conventional standard leads and should always be evaluated in conjunction with the latter.

PICK

Sandberg, A. A., Wener, J., Master, A. M., and Scherlis, L.: Intermittent and Transient Bundle Branch Block: A Clinical and Electrocardiographic Study. Ann. Int. Med. **35:** 1085 (Nov.), 1951.

The cases included in this report consist of 12 persons who at one time or another showed transient or intermittent bundle branch block. In seven cases, various procedures were carried out in an effort to cause either bundle branch block or normal conduction to appear, depending upon the control record. These maneuvers included the two-step exercise test, anoxemia test, breathing of 100 per cent oxygen for 20 minutes, changes in posture, respiratory maneuvers, inhalation of amyl nitrite, and carotid pressure. In several of the patients esophageal records were obtained.

From the available data, it is apparent that the pattern of bundle branch block, either right or left, can be present because of many factors. A localized permanent lesion to a bundle branch need not be the only explanation when such a pattern is seen. Other disturbances, such as tachycardia, infection, cardiac failure, pulmonary embolism, positional and respiratory effects, anoxemia, anemia and metabolic derangement when superimposed on an already diseased heart, may embarrass the conductive ability of specialized tissue and be responsible for the development of an intraventricular conduction defect.

It is difficult to determine accurately the frequency with which the pattern of bundle branch block can be ascribed to a permanent lesion of a bundle branch completely interrupting conduction in this branch. Additional impairment to conduction in an already diseased heart may be sufficient to depress conduction and result in the pattern of bundle branch block. All patients whose electrocardiograms reveal the pattern of bundle branch block should be subjected to several procedures, if their condition permits, to ascertain whether normal intraventricular conduction can be restored. Such procedures may include carotid pressure, breathing of 100 per cent oxygen, digitalization if failure is present, and correction of anemia. In this way, it may be possible to determine whether the bundle branch block is due to a permanent unalterable involvement of the conductive system or whether the condition defect is essentially functional in character.

WENDKOS

Scott, J. C., and Reed, E. A.: Electrocardiographic Effects of Reflex Vagal Stimulation. Am. J. Physiol. **167:** 551 (Nov.), 1951.

The authors used increased carotid sinus pressure and cooling of the pacemaker to slow heart rate. Changes in amplitude of P and duration of P-R and R-R intervals were due to vagal impulses which were independent of sympathetics when carotid sinus pressure was elevated. The relation between R-R and the corresponding P-R interval is linear. Unilateral vagotomy or bilateral sympathectomy does not change this relationship. Effects of local cooling and reflex vagal effects are additive on P amplitudes and R-R durations. Nodal rhythms due to cooling the SA node may be reduced by carotid sinus stimulation.

OPPENHEIMER

Frischknecht, W.: Alterations of the Electrocardiogram without Myocardial Disease in Childhood. Acta paediat. Helv. **5:** 443 (Nov.), 1951.

The author compared the incidence of electrocardiographic abnormalities in 2000 consecutive children admitted to a children's hospital, with that among 1000 army pilots, and found both groups to be similar. The electrocardiogram in childhood is subject to the same alterations by positional, neurogenic, hormonal and humoral factors as in the adult. This is illustrated by tracings obtained in children in orthostatic conditions, before and following injection of sympathomimetic drugs, and under treatment with various hormones. The author stresses the danger of diagnosing heart disease in children only on the basis of electrocardiographic abnormalities, without consideration of the above-mentioned factors.

PICK

HYPERTENSION

Bretschger, E.: The Absolute and Relative Frequency of Renal Hypertension and the Under-

lying Kidney Diseases. Cardiologia **19:** 182 (fasc. 3), 1951.

The author attempted to demonstrate the relationship between kidney disease and hypertension on a statistical basis in a large autopsy material. Among 2610 cases analyzed, 676 (26 per cent) had evidence of hypertension and 315 (12 per cent) some type of kidney disease. In the hypertensive group without kidney disease, a break-down according to age revealed an unquestionable relation between higher age and incidence of blood pressure elevation. Kidney disease was four times as frequent in hypertensives as in normotensive cases, suggesting a causal connection between the two diseases. However, in half of the cases with a combination of hypertension and kidney disease, the possibility of an extrarenal etiology of the hypertension could not be ruled out.

The study, therefore, failed to establish a definite relationship between pathology and hypertension. However, the presence of a unilateral kidney affection in 49 cases (7.5 per cent of the total number of hypertensives) suggested the possibility that the kidney affection could have been diagnosed in time by a routine urologic examination, and that the patients might have been cured of hypertension by unilateral nephrectomy.

PICK

Evans, J. A., Rubitsky, H. J., Bartels, C. C., and Bartels, E. C.: Re-evaluation of the Reliability of Pharmacologic and Cold Pressor Studies in Hypertension and Pheochromocytoma. Am. J. Med. **11:** 448 (Oct.), 1951.

The authors review their large experience with the use of currently employed tests for the diagnosis of pheochromocytoma in hypertensive patients. Included are cold pressor response, Mecholyl, histamine, tetraethylammonium, Dibenamine, and Benzodioxane. Ten milligrams of Mecholyl is the best, safest, and simplest screening provocative test. Histamine gave frequent false positives in patients with essential hypertension. Although Dibenamine gave 37 per cent incidence of probable false positive tests, it was useful as a check on positive provocative tests. Benzodioxane was of value despite pressor responses occurring not only in the usual hypertensive syndromes, but also in paroxysmal hypertension due to pheochromocytoma.

HARRIS

Aronson, N., Stern, G. S., and Cohlan, S. G.: Paroxysmal Hypertension Simulating Pheochromocytoma. Pediatrics **8:** 664 (Nov.), 1951.

The authors report an 8 year old girl with attacks of paroxysmal hypertension and vomiting; the administration of Benzodioxane induced a decrease in blood pressure. Since it was strongly suspected that this patient had a pheochromocytoma, an extensive exploratory laparotomy was done, with negative results. There were, however, some unusual characteristics including diminished lacrimation, excessive drooling, increased perspiration, frequent blotching of the skin, and crying without tears. This group of signs plus the cyclic vomiting and hypertension were considered indications of an unusually labile autonomic nervous system.

A younger sibling also had labile blood pressure, but did not exhibit the periodic attacks of vomiting and hypertension. Dibenamine, Banthine, Eumydrine, Dramamine, adrenocorticotropic hormone (ACTH), and cortisone were studied for their effects on the patient's signs and symptoms with no evidence of therapeutic value.

A series of children with similar symptoms were recently described. In two of these patients a search was made for a pheochromocytoma without success. It is concluded that this clinical entity is due to an autonomic nervous system dysfunction which is unrelated to a pheochromocytoma.

MARGOLIES

Schottstaedt, M. F., and Sokolow, M.: Natural History and Course of Malignant Hypertension. Am. J. Med. **11:** 626 (Nov.), 1951.

One hundred four cases of malignant hypertension were studied. Papilledema in the presence of severe hypertension was accepted as the criterion for diagnosis. The average survival after the discovery of papilledema was 13 months in patients with good renal function and four months in those with impaired renal function. In 10 cases, renal impairment developed in an average of four and four-tenths months. Autopsies in 31 cases revealed the basic renal lesion to be neprosclerosis in twelve, pyelonephritis in 12, and glomerulonephritis in 7. Other patients in whom papilledema disappeared survived more than 30 months. With the exception of one patient with glomerulonephritis, none in whom papilledema disappeared died of renal insufficiency.

Disappearance of papilledema indicates a decrease in tempo of malignant hypertension and reversal to benign hypertension. Early and vigorous treatment is essential in malignant hypertension before renal function is impaired and before irreparable damage to cerebral and cardiac vessels has occurred.

HARRIS

Ledingham, J. M.: The Nature of the Hypertension Occurring in the Nephrectomized Parabiotic Rat. Clin. Sci. **10:** 423 (Nov.), 1951.

Total nephrectomy in one of a pair of parabiotic rats almost always produced hypertension in that member, but not in the intact one. Unilateral nephrectomy in both members of a pair was only rarely followed by hypertension in either, but when the remaining kidney was removed the totally nephrectomized member developed hypertension. Arteriolar lesions occurred in the viscera of nephrectomized

members as a rule, but not in intact members. The hypertension induced by nephrectomy was abolished by total adrenalectomy in that member. Simultaneous excision of kidneys and adrenals was not followed by hypertension, but when DOCA (desoxycorticosterone acetate) pellets were implanted in these animals hypertension occurred. When DOCA was implanted in the intact member of such a pair, a lesser rise in blood pressure was found. Evidence is advanced that the hypertension produced by the above methods may be caused by pressor substances from the adrenals which are normally eliminated by the kidneys.

ENSELBERG

Floyer, M. A.: The Effect of Nephrectomy and Adrenalectomy upon the Blood Pressure in Hypertensive and Normotensive Rats. Clin. Sci. **10:** 405 (Nov.), 1951.

Corroboration was obtained of previously reported work which showed that partial occlusion of one renal artery by a clip resulted in hypertension followed by vascular changes in the untouched kidney, and that removal of the clipped kidney did not restore normal blood pressure. Removal of the clip resulted in persistence of hypertension in about half of the rats, but removal of the untouched kidney was followed by return of normal blood pressure.

When hypertension had been produced by this method and both kidneys were subsequently removed, hypertension persisted. Total adrenalectomy restored normal blood pressure in rats made hypertensive by renal artery occlusion or nephrectomy, but the hypertension returned after administration of 1.0 per cent sodium chloride. Several hypothetic explanations of these findings are offered, and the possibility is considered that the electrolyte balance in muscle cells of the cardiovascular system is the fact which controls blood pressure.

ENSELBERG

Leonards, J. R., and Heisler, C. R.: Artificial Kidney. IV. Maintenance of Life in Bilaterally Nephrectomized Dogs and Its Relation to Malignant Hypertension. Am. J. Physiol. **167:** 553 (Nov.), 1951.

The authors used the artificial kidney to prolong the life of bilaterally nephrectomized dogs to nine and one-half days as compared to six and six-tenths days for untreated controls. Both sets of animals were fed an electrolyte free diet of sucrose and oleomargarine supplemented by 10 per cent glucose intravenously. Although the animals maintained with artificial kidney remained in good condition up to the last one to two days, only one developed a high blood pressure during its last two days. It is concluded that bilateral nephrectomy alone is not a sufficient condition for the development of hypertension.

OPPENHEIMER

Friedman, M., Rosenman, R. H., and Freed, S. C.: Depressor Effect of Potassium Deprivation on the Blood Pressure of Hypertensive Rats. Am. J. Physiol. **167:** 457 (Nov.), 1951.

Rats were made hypertensive by unilateral nephrectomy combined with a figure-eight silk ligature placed about the poles of the remaining kidney. Hypertensive rats placed on a diet essentially free of potassium had a large decrease in pressure to normal or subnormal values. Adrenals, kidney and heart showed histologic changes known to occur in potassium deficiency. The authors do not consider the cardiac findings sufficient to account for the fall in blood pressure.

OPPENHEIMER

PATHOLOGIC PHYSIOLOGY

Wilson, Russell, Borden, Craig, W., and Ebert, R.: Adaptation to Anoxia in Chronic Pulmonary Emphysema. Arch. Int. Med. **88:** 581 (Nov.), 1951.

A study was made of the adaptation to anoxia in patients with pulmonary emphysema. In contrast to residents of high altitudes, an increase in the hemoglobin content of the blood was seldom observed in patients with pulmonary emphysema and anoxia. Moreover, there was no evidence of increased activity of the bone marrow in 14 patients studied. The reason for this failure of hematologic adaptation to anoxia is not established, but it may be related to the presence of chronic bronchial infection. On the other hand, an increase in the mean corpuscular volume regularly occurs in these patients and is apparently the result of anoxia.

Breathing oxygen reduces the resting level of ventilation and leads to an increase in the carbon dioxide tension and a reduction of the pH of the arterial blood in patients with pulmonary emphysema and anoxia. Anoxia serves as an important stimulus to ventilation in these patients, and removal of this stimulus by means of oxygen therapy may result in coma associated with uncompensated respiratory acidosis. Increase in cardiac output does not appear to be an important means of adaptation to anoxia in pulmonary emphysema.

BERNSTEIN

Maier, H. C., Rich, G. W., Eichen, S.: Clinical Significance of Respiratory Acidosis During Operations. Ann. Surg. **134:** 653 (Oct.), 1951.

An attempt was made in patients subjected to major surgical procedures to correlate the carbon dioxide alterations in arterial blood with the course of the anesthesia, the conduct of the operation, the pulmonary status of the patient, and the occurrence of large blood loss or of cardiac arrhythmias.

It was found that within 10 or 15 minutes after the inhalation anesthesia was started, a moderate degree of acidosis was sometimes present. This type of response was observed more often in patients

with pulmonary disease, especially emphysema. A difficult induction or intubation caused alarming degrees of hypoxia.

It was believed that the decreased ventilatory exchange of the anesthetized patient was responsible for both the hypoxia and the acidosis. This was particularly true when anesthetic gases were administered with positive pressure in a closed system, as in the case of operative procedures in the thorax.

ABRAMSON

Denton, D. A., Wyan, V., McDonald, I. R., and Simon, S.: Renal Regulation of the Extracellular Fluid. II. Renal Physiology in Electrolyte Subtraction. Acta med. scandinav. Suppl. **261:** 1, 1951.

The physiology of the kidney, particularly in the realm of electrolyte regulation is dealt with exhaustively in this monograph. It is shown that if Na^+ (sodium ion) is subtracted from the body in excess of Cl^- (chloride ion), relative to the extracellular ratio of these two ions, the ratio Cl/Na remains constant because the kidney excretes Cl^- in excess of Na^+, commensurately with the stress. However if Cl^- is lost from the extracellular fluid in excess of Na^+, relative to the extracellular ratio of these two ions, the extracellular Cl/Na ratio falls, because the kidney fails to excrete Na^+ in excess of Cl^-. In this situation, infusion of saline may cause the extracellular Cl/Na ratio to return to normal.

The presence of a biologically inactive anion (HCO_3^-) which is produced in the body is considered the basic reason for the difference in renal behavior in these two situations; no mechanism is present for the production of a biologically inactive cation. There is evidence to suggest that renal behavior is different in excess Na^+ subtraction (as with a postgastrectomy duodenal fistula) than in anion addition acidemia or respiratory acidemia. The authors believe it may be inferred that the Cl/Na ratio of the glomerular filtrate directly influences the tubular behavior in excess Na^+ subtraction. It is emphasized that "normal" saline is under most circumstances an electrolyte pattern distortion stress and its indiscriminate use can be prejudicial to the patient in conditions such as an excess Na^+ subtraction, and anion addition acidemia such as diabetic coma, and anuria.

ROSENBAUM

Abrams, W. B., Lewis, D. W., Bellet, S.: The Effect of Acidosis and Alkalosis on the Plasma Potassium Concentration and the Electrocardiogram of Normal and Potassium Depleted Dogs. Am. J. M. Sc. **222:** 506 (Nov.), 1951.

The authors employed 4 per cent ammonium chloride and 5 per cent sodium bicarbonate solutions to produce metabolic acidosis or alkalosis respectively in a group of dogs in order to correlate the disturbances in acid-base balance with the plasma potassium concentration and the electrocardiogram. Potassium depletion was then accomplished by the administration of desoxycorticosterone acetate whereupon acidosis and alkalosis were again induced and the observations repeated. Ammonium chloride caused a sharp fall in pH and CO_2 combining power with an increase in serum potassium in both the normal and potassium depleted animals. The hematocrit was not changed. A rise in the serum phosphate values was noted. An increase in the amplitude of the T waves was noted in both groups of acidotic dogs in association with these biochemical alterations. Sodium bicarbonate produced a rise in the pH and CO_2 combining power in the normal dogs but showed less striking changes in the potassium depleted animals. The hematocrit fell slightly and there was very little change in phosphate levels. In both groups the potassium concentrations decreased. The electrocardiograms showed a decrease in amplitude and notching of the T waves in the alkalotic dogs.

A linear inverse relationship between the pH values and the serum potassium concentrations was apparent in this study and the latter changes were adequately reflected in the T waves of the electrocardiograms. Alterations in acid-base balance apparently influence the rate of transfer of potassium from cell to serum and may also influence the renal excretion of potassium both in normal and potassium-depleted animals.

SHUMAN

Duff, R. S.: Circulatory Changes in the Forearm Following Sympathectomy. Clin. Sc. **10:** 529 (Nov.), 1951.

The author describes a plethysmographic method for measuring blood flow in the forearm and hand. Using this method, changes in flow were followed in limbs after sympathectomy for hyperhidrosis and for Raynaud's disease. Blood flow in the forearm increased immediately after sympathectomy, reaching a peak (about 300 per cent increase) in 24 hours and lasting three or four days. In the hand the increased flow was of greater degree, especially in hyperhidrotic limbs, but took about two days to reach a peak, and lasted two or three days longer. The smaller rise in Raynaud cases may have been due to organic changes in digital vessels.

The pattern of response of forearm and hand to sympathectomy is sufficiently alike to suggest that the recovery of tone in both vascular beds is in response to similar factors. It is to be noted that the forearm contains over four times as much muscle as skin, and the hand contains twice as much skin as muscle. Thus, the increase in forearm blood flow is probably due to dilatation of muscle vessels.

ENSELBERG

Howard, P., and Leathart, G. L.: Changes of Pulse Pressure and Heart Rate Induced by Changes of

Posture in Subjects with Normal and Failing Hearts. Clin. Sc. **10:** 521 (Nov.), 1951.

Observations were made on 43 subjects during tilting from 10 degrees above horizontal to 15 degrees below vertical. Direct arterial blood pressures were measured. The normal response to tilting from almost horizontal to almost vertical positions was a decrease in pulse pressure and an increase in heart rate averaging 17 per cent and 12 per cent respectively. Very similar changes were found in subjects with compensated heart disease.

On the other hand, subjects with left heart failure showed increases in pulse pressure and either a fall in heart rate or no change. Three cases of cor pulmonale as well as 22 additional normal students all showed normal responses to tilting. It is possible that the response of the decompensated patients was analogous to that produced by application of thigh cuffs or bleeding. These result in increased cardiac output, resembling the behavior to the overloaded heart-lung preparation.

ENSELBERG

Holland, G. C., and Stead, E. A.: Effect of Vasopressin (Pitressin) Induced Water Retention on Sodium Excretion. Arch. Int. Med. **88:** 571 (Nov.), 1951.

The effect of vasopressin injection (Pitressin) on the excretion of water, sodium, chloride, and potassium was studied in normal subjects. After the osmotic stimulus to the production of antidiuretic hormone was removed by electrolyte excretion or intake of water, the hourly rate of water excretion became variable.

These data suggest that during ordinary activity the secretion of antidiuretic hormone is influenced more by reflex than by osmotic stimuli. When variations in the effect of antidiuretic hormone on the renal tubules are reduced to a minimum by repeated injection of vasopressin, hourly rates of water excretion show much less variation. Under these conditions the amount of water excreted is influenced by the rate of sodium excretion. Vasopressin injection had no demonstrable effect on the excretion of sodium, chloride, and potassium in the subjects receiving hypertonic and isotonic sodium chloride solutions.

The data suggest that neither vasopressin nor endogenously produced antidiuretic hormone will produce the picture of sodium retention seen in congestive heart failure.

BERNSTEIN

Nickerson, J. L., Cooper, F. W., Jr., Robertson, R., and Warren, J. V.: Arterial, Atrial and Venous Pressure Changes in the Presence of Arteriovenous Fistula. Am. J. Physiol. **167:** 426 (Nov.), 1951.

There is no agreement on venous pressure changes which take place when an arteriovenous fistula is opened or closed. The present study provides additional information. The rise in pressure in the general venous bed is small when a fistula is opened. This rise is of the order of 0.5 mm. Hg, but this constitutes an increase in the venous gradient of 25 per cent. Decrease in arterial pressure permits the left ventricle to empty more completely. The fall in pressure results from the escape of arterial blood through the fistula. Since the left side is more completely emptied it provides more room for the right heart to empty into it. This in turn gives more space for the inflow from the venous bed. In the region of the fistula the markedly increased arteriovenous gradient provides blood for the increased circulation. Venous pressures rise markedly at the level of the fistula, but become less further up the venous bed toward the atrium.

OPPENHEIMER

Fowler, N. O., Westcott, R. N., and Scott, R. C.: Disturbances in Cardiac Mechanism of Several Hours Duration Complicating Cardiac Venous Catheterization. Am. Heart J. **42:** 652 (Nov.), 1951.

In 110 consecutive cardiac catheterizations disturbances in cardiac mechanism persisted in nine patients following withdrawal of the catheter. Right bundle branch block was present in seven cases, auricular fibrillation in one, and frequent ventricular premature beats in the other. These disturbances disappeared within 12 hours. The authors emphasize the necessity of constant fluoroscopic and direct-writing electrocardiographic observations during cardiac catheterization.

HELLERSTEIN

Gitelson, S.: The Influence of Body Posture on the Antecubital Venous Pressure. Cardiologia **19:** 163 (fasc. 3), 1951.

The author reports investigations on differences of the venous pressure in a 45 degree sitting position and in a supine position. The study included 31 patients with various types of heart disease, 15 of them in failure, and eight control persons without cardiovascular disease.

In nearly all patients with severe heart failure associated with elevation of the venous pressure, the latter was significantly lower in supine position. In the majority of cases with mild heart failure and normal venous pressure, the values were practically equal (differences less than $\pm$ 2 cm. water) in both positions. Similar conditions were found in elderly persons and in cases of arteriosclerosis without heart failure. In cases with arterial hypertension, the venous pressure in sitting position was higher than that in supine position. In patients without cardiovascular disease no definite relationship was found between the respective values.

In patients with heart failure, the differences of venous pressure values in the two positions diminish

with fall of the venous pressure following treatment, and disappear when the venous pressure becomes normal. Readings in the two positions provide, therefore, a fair estimate of the degree of heart failure present, and of the response to therapy.

PICK

Houck, C. R.: Alterations in Renal Hemodynamics and Function in Separate Kidneys during Stimulation of Renal Artery Nerves in Dogs. Am. J. Physiol. **167:** 523 (Nov.), 1951.

Renal artery nerves of the left kidney were stimulated and the other kidney served as a control. There was no shunting of blood from cortex to medulla as demonstrated in the rabbit by Trueta. Ischemia and hyperemia involved both cortex and medulla. Filtration rate, urine flow, blood flow, maximum tubular excretory capacity for para-aminohippuric acid and for glucose extraction percentages of creatinine and para-aminohippuric acid, filtration rate per unit of tubular excretory tissue and perfusion of active tubules with blood were all decreased. Filtration rate per unit of tubular reabsorptive tissue and extraction percentage of oxygen were increased. When infarcts were seen in the stimulated kidney, both cortex and medulla were involved.

OPPENHEIMER

Peters, N. S., Newman, W. and Burstein, C. L.: Electrocardiographic Studies During Endotracheal Intubation. IV. Effects During Cyclopropane or Cyclopropane-Ether Anesthesia and Intravenous Procaine Amide. Anesthesiology **12:** 673 (Nov.), 1951.

Electrocardiograms were taken on 100 patients who had endotracheal intubation during cyclopropane or cyclopropane-ether general anesthesia. A 300 mg. dose of procaine amide was administered intravenously one to five minutes prior to intubation. Electrocardiographic disturbances were found in 17 patients at the time of endotracheal intubation. There were 13 instances of sinus tachycardia, three of ventricular premature beats and one of nodal rhythm. In a comparable group of patients who had not received procaine amide prior to intubation, electrocardiographic disturbances were observed in more than 60 per cent of patients. The authors suggest that hypoxia, insufficient depth of anesthesia and repeated attempts at intubation are some of the factors which precipitate the reflexogenic cardiac disturbances.

SAGALL

PATHOLOGY

Zoli, A.: Parietal Fibroplastic Endocarditis with Blood Eosinophilia. Cardiologia **19:** 139 (fasc. 2), 1951.

A case is described of a 31 year old man with a history of several allergic manifestations, who developed an acute tonsillitis, followed by myocardial involvement, and died within a year with signs of progressive chronic heart failure. During the course of his illness, pronounced eosinophilia (30 to 50 per cent) was observed, though during the last few days before death the figures dropped to normal.

At postmortem a parietal fibrotic endocarditis was found involving the endocardium of both ventricles and of the right auricle, while the valves were completely intact. The outstanding histologic features were hyaline fibrosis of the endocardium, and interstitial myocarditis with granulomatous foci containing numerous eosinophil cells and showing fibrinoid degeneration. Infiltration with eosinophils was also present in the liver and spleen, in addition to chronic congestion. In the bone marrow eosinophil myelocytes and leukocytes were predominating.

The author feels that in view of the pronounced eosinophilia, the case represents an instance of an allergic disease with particular immunologic conditions. The unusual clinical course can be attributed to the unusual localization of the pathologic changes. The case is classified by the author as an instance of generalized collagen disease "related to endocarditis lenta and to eosinophilic rheumatic vasculitis."

PICK

Goodwin, J. F., and Petrie, E.: Insidious Thrombosis of the Abdominal Aorta. Brit. Heart J. **13:** 554 (Oct.), 1951.

A man, 49 years old, complained of frontal headaches of three months duration, at times accompanied by nausea and vomiting. Physical examination revealed a blood pressure of 210/100 in both arms and 140/80 in the thighs. There was no evidence of a collateral circulation. The buttocks and lower limbs were lacking in muscle mass.

A retrograde aortagram revealed a "rat tail" constriction and termination of the dye in the aorta at the level of the third lumbar vertebra. A thoracolumbar sympathectomy was carried out. From the origin of the renal arteries, the aorta was pulseless and thrombosed. Twelve weeks later, the patient was free of headaches but developed pain in the muscles of both thighs after walking 100 yards. This development is attributed to orthostatic hypotension.

The symptoms in this case are unusual. In a review of 25 previously reported cases of thrombosis of the abdominal aorta, early symptoms consisted of intermittent claudication of the calves or an ache in the hips and thighs on walking. Trophic changes in the lower limbs were common.

SOLOFF

Radding, R. S.: Ball Thrombus of the Right Auricle. Am. J. Med. **11:** 653 (Nov.), 1951.

The author reports the second instance of ball

thrombus of the right auricle in a total of 29 authenticated cases of ball thrombus involving different chambers of the heart. His case is associated with acute bacterial endocarditis due to Friedlander's bacillus. This condition occurs predominantly in females who, in all save one case, had associated rheumatic heart disease or mitral disease. The diagnosis of intracardiac thrombosis of the left heart is to be suspected when progressive peripheral ischemia, particularly of the lower extremities, develops in patients with mitral disease. Involvement of the right heart should be suspected when the clinical aspects of right ventricular failure are complicated by dusky cyanosis, air hunger, and a rapidly changing clinical picture.

HARRIS

Denst, J., Hurst, A., and Dressler, S. H.: Histologic Study of the Blood Vessels in Surgically Resected Tuberculous Lungs. Am. Rev. Tuberc. **64:** 489 (Nov.), 1951.

Following the observation that cardiac catheterization revealed pulmonary hypertension in most tuberculous patients selected for lung surgery, the writers studied the vascular changes in the surgical specimens. They wished to correlate them with the pulmonary hypertension, and to determine the possible role of previous collapse therapy. They examined the lung specimens from 85 patients, 39 of which had undergone pneumonectomy. Twelve patients never had previous collapse therapy of any type.

The majority revealed significant vascular changes, more so than anticipated. Intimal thickening ranging up to endarteritis obliterans was the common lesion. These changes were more pronounced in scar tissue. Direct classical involvement by tuberculosis was seldom noted; it occurs, in the writers' opinion, only in overwhelming infection. The lesions in small vessels were similar to those in emphysema; yet their abundance in proximity to active tuberculous lesions speaks for a toxic factor.

The incidence of these vascular changes is greater in lungs treated previously by collapse therapy, particularly by long-standing thoracoplasty. The pulmonary artery pressure is usually only moderately elevated in these cases. Sometimes it is normal with the patients at rest but almost always elevated by moderate exercise. While the vascular changes are common, a direct relationship between them and the degree of pulmonary hypertension is not yet apparent.

GOULEY

PHARMACOLOGY

Doull, J., Herrmann, R. G., Geiling, E. M. K., and Dubois, K. P.: Effects of Bufagin on the Respiration of Cardiac Muscle and Other Tissues. Arch. internat. pharmacodyn. **86:** 487, 1951.

In preliminary studies it has been found that high concentrations of bufagin produced a marked inhibition of respiration of heart and brain slices in vitro (Dubois, Doll and Geiling: Fed. Proc. **8:** 287, 1948). In the present investigation, the organs of rats, mice and guinea pigs were used. The tissues were removed immediately after sacrificing the animal and slices weighing about 100 mg. were placed into the Warburg vessel. Bufagin was obtained from the venom of the tropical toad. When the medium contained a high concentration of calcium, bufagin caused a stimulation of respiration in heart muscle slices of guinea pigs. This persisted for two hours and was followed by a decrease to values below normal. When the medium did not contain added calcium only a depressant action by bufagin on respiration was observed. Slices of the heart of rats or mice were less sensitive to the action of bufagin. Respiration of brain slices was inhibited by lower concentrations of bufagin, while slices from the kidney and liver were relatively insensitive. The enzyme systems of succinic dehydrogenase and cytochrome oxidase were not influenced by saturation of the system with bufagin.

SCHERF

Berry, K., Garlett, E. L., Bellet, S., and Gefter, W. I.: Use of Pronestyl in the Treatment of Ectopic Rhythms. Am. J. Med. **11:** 431 (Oct.), 1951.

Pronestyl administered to 78 patients with ventricular tachycardia, nodal tachycardia, paroxysmal auricular tachycardia, or multiple ventricular premature contractions effectively converted a large proportion of these arrhythmias to normal. Pronestyl was notably ineffective in converting auricular flutter or fibrillation to normal. Oral administration of pronestyl is the method of choice. The intravenous preparation should not be given faster than 100 mg. per minute. Pronestyl is safer than quinidine when the corresponding effective dose is given intravenously.

The most serious toxic manifestation is the development of hypotension, which produced coronary insufficiency in two patients and convulsive seizures in two others. Two patients developed definite psychoses and a third went into a severe mental depression. Hypotension is most frequently observed after intravenous use of pronestyl. Four patients in extremis died during or within 45 minutes after intravenous injection of pronestyl. It was difficult to ascertain whether the drug was directly implicated in the death of these patients.

Electrocardiographic effects following the administration of pronestyl include prolongation of P-R and Q-T, flattening of the T wave, and widening of QRS. Considerable widening of QRS is an indication for cessation of therapy. Peak effect after pronestyl administration, as measured by an increase in Q-T_c, is noted four minutes after the end of

intravenous injection and one to two hours after oral medication.

HARRIS

Kaufman, J., Iglauer, A., and Herwitz, G. K.: Effect of Isuprel (Isopropyl-epinephrine) on Circulation of Normal Man. Am. J. Med. **11**: 442 (Oct.), 1951.

Isuprel, a useful agent in the treatment of bronchial asthma, consistently increased the cardiac output and pulse pressure of patients after subcutaneous administration. These effects were less marked after sublingual administration of Isuprel and absent after aerosol inhalation. The authors advise caution in the use of Isuprel in asthmatic patients with cardiovascular disease since the cardiovascular effects after subcutaneous administration of Isuprel may be as marked as those produced by epinephrine.

HARRIS

Schroeder, H. A.: Use of Diuretic Agents. J. A. M. A. **147**: 1109 (Nov. 17), 1951.

The author approaches the problem of diuretic agents both by means of a table and a text discussion of individual effects of various agents. He explains the diuretic effect of water, alcohol, osmotic diuretics, neutral substances, plasma oncotic affectors, xanthines, mercurials (both with and without theophylline), digitalis, thyroid, and parathyroid substances.

Water is to be principally used in the individual who is dehydrated and has high electrolyte content in his blood. Alcohol is indicated in overhydration. Normal saline solution is useful in dehydration with normal electrolytes. Concentrated salt solution is used in overhydration with low electrolytes. Potassium salts are useful in edema with normal electrolytes. Urea and acidifying salts are used in edema where fair to good renal reserve is present. The plasma oncotic affectors (serum albumin) are used in cases with hypoproteinemia. Xanthines, chiefly theophylline, are used in edema with normal electrolytes and they should be used with caution where cardiac arrhythmias are present. The mercurial diuretics are used where there is edema with normal electrolytes and fair renal reserve. Mercurials containing theophylline should be used with caution if cardiac arrhythmias are present and the diuretic is given by parenteral means. Digitalis is useful in edema due to myocardial failure and acts by improving the efficiency of the myocardium.

Schroeder points out that the best results with diuretics are obtained when one first determines the cause of the edema and then elects the proper diuretic to remove it.

KITCHELL

Gelfand, M. L.: Visual Symptoms After Digitoxin Therapy. J. A. M. A. **147**: 1231 (Nov. 24), 1951.

Gelfand presents four cases who were given digitoxin because of cardiac failure. Toxic visual symptoms occurred in all four. All were given the full digitalizing dose of 1.2 mg. in a maintenance dose of 0.2 mg. daily. The visual symptoms consisted of blurring of vision, white and yellow vision, scotoma, bright flickering lights, and "objects covered with snow." The complaints developed between the fourth and twelfth day of therapy. Cessation of administration of the drug for several days cleared these disturbances and reintroduction of small maintenance doses produced no ill effect. No disturbances of the cardiac mechanism were noted in this group of patients.

KITCHELL

Grossman, J., Weston, R. E., Lehman, E. A., Halperin, J. P., Ullman, T. D., and Leiter, L.: Urinary and Fecal Excretion of Mercury in Man Following Administration of Mercurial Diuretics. J. Clin. Investigation **30**: 1208 (Nov.), 1951.

The excretion of mercury, following Thiomerin (2 ml. intravenously or subcutaneously) or Mercuhydrin (2 ml. intramuscularly), was studied in 17 patients, 13 of whom were in congestive heart failure. As a result of early rapid excretion of mercury, half of the total dose appears in the urine within two and one-half to three hours. From 60 to 95 per cent of the injected mercury is excreted in the urine during the first 24 hours and mercury may appear in the urine for the next day or two. Fecal excretion was very small, except in one patient with renal insufficiency whose urinary output was considerably reduced. Mercury excretion after subcutaneous injection was reduced during the first 30 to 60 minutes when compared to the intravenous route.

Urinary mercury excretion tends to remain fairly constant, despite wide fluctuations in diuresis. Neither ammonium chloride nor desoxycorticosterone acetate affected the excretion of mercury.

Since an appreciable fraction of the administered mercury cannot be accounted for, even though urinary and fecal excretion is followed for a number of days, it is concluded that the daily administration of 2 ml. of a mercurial diuretic would inevitably lead to the accumulation of mercury in the body. The clinical significance of this observation is not certain at present.

WAIFE

Gootnick, A., Lipson, H. I., and Turbin, J.: Inhalation of Ethyl Alcohol for Pulmonary Edema. New England J. Med. **245**: 842 (Nov. 29), 1951.

Ethyl-alcohol inhalation is effective in experimental pulmonary edema, presumably due to alteration of the surface tension at the fluid-air interface, thereby collapsing the foam bubbles, and to the volatility of the alcohol which permits penetration into the finer air spaces.

Technical difficulties in administering alcohol by

inhalation were overcome by the use of a single tank from which oxygen is passed through a simple vaporizer. It consists of an 8-ounce bottle containing 4 ounces of 50 per cent ethyl alcohol, with a rubber stopper fitted with two large-bore metal tubes. One of these tubes delivers oxygen to the bottom of the bottle so that it bubbles through the alcohol whereas the other tube is above the fluid level so that it carries alcohol-laden oxygen to the meter mask. All sprayers and filters are removed so that loss of pressure is minimized.

The strikingly beneficial effects of treatment of acute pulmonary edema with ethyl alcohol inhalation in a patient with an acute myocardial infarction and in a second patient whose edema appeared after operation for constrictive pericarditis are described in detail. These patients had not responded to more conventional measures. The authors report that no adverse systemic effects of alcohol have been noted in the patients they have studied.

ROSENBAUM

Miles, H. H. W., and Cobb, S.: Neurocirculatory Asthenia, Anxiety and Neurosis. New England J. Med. **245:** 711 (Nov. 8), 1951.

The authors disagree with the definition of neurocirculatory asthenia as it is commonly employed because it includes a variety of psychoneurotic illnesses under a single heading. It is their belief that although such usage may make diagnosis simple, it is an impediment to further understanding of psychologic and physiologic mechanisms in the production of these disorders. It is believed that some patients' major symptoms are the result of an inherited or developmental (physiologic) abnormality, while others have difficulties which are purely psychogenic in origin. The majority represent an admixture of these two elements in varying degrees. Although there are symptomatic resemblances, investigators in this field are urged to recognize the psychodynamic differences which exist in them.

ROSENBAUM

Brown, B. B., and Acheson, G. H.: Some Actions of Procaine and Related Compounds on the Dog's Auricle and A-V Connections. J. Pharmacol. & Exper. Therap. **103:** 269 (Nov.), 1951.

The authors studied the effects of three active compounds, procaine, diethylaminoethanol (DEAE), and diethylamonoethyl 2,4-dichlorobenzoate (DCB) on several properties of the dog's auricle; namely, the conduction velocity of the auricular wave between two points and the threshold voltage of a short electric shock. They stimulated the tip of the exposed auricle of the anesthetized dog and then recorded electrograms at distant auricular spots.

Auricular conduction velocity was studied as a function of auricular rate. Procaine (8 mg. per kilogram) decreases conduction velocity at all rates, whereas DEAE (32 mg. per kilogram) and DCB (8 mg. per kilogram) decrease it principally at high rates. The threshold voltage was determined at different rates of stimulation of the auricle. Procaine increases thresholds only at high auricular rates, whereas DEAE and DCB increase them at all rates. The maximal rate at which the auricle will respond, when driven by impulses conducted from a distant, stimulated auricular site, is decreased by procaine, DEAE, and DCB.

The ventricular rate was studied as a function of auricular rate. Procaine improves the ability of the ventricle to follow the auricle in the innervated heart but impairs it after decentralization. Procaine, however, blocks the effects of vagal or sympathetic stimulation. DEAE and DCB impair the ability of the ventricle to follow the auricle in innervated or decentralized hearts and do not effectively block the effects of stimulating the nerves.

RINZLER

Stokes, J. H., Wolferth, C. C., Edeiken, J., Falk, M. S., and Ford, W. T.: Treatment of Cardiovascular Syphilis. J. A. M. A. **147:** 944 (Nov. 3), 1951.

The authors discuss the efficacy of penicillin in cardiovascular syphilis in studies based on 111 cases. Although they recognize that the conditions of control and observational follow-up in this series cannot be adequate, they make the following tentative conclusions.

There is little evidence that significant therapeutic shock occurs in the full dosage use of crystalline penicillin G without conventional heavy metal "preparation." There is no evidence of vascular toxic effect or of therapeutic paradox. Anginal pain was relieved and penicillin was admirably tolerated by the decompensated heart.

The advocated treatment includes hospitalization, two-hour schedule, crystalline penicillin G 4,800,000 to 9,600,000 units in 40,000 to 80,000 unit individual doses, but procaine penicillin on a 600,000 unit single or 300,000 unit two-injection daily schedule can be given. The authors feel that repetition of courses in excess of two of 9,000,000 units each seems unnecessary. Blood serologic results are virtually nil as might be expected with late syphilis. The concomitant or subsequent use of heavy metal seems, on general experimental grounds, to be unnecessary.

KITCHELL

Simson, J., and Bunim, J. J.: The Anti-Rheumatic Effect of 3-Hydroxy-2-Phenylcinchoninic Acid (HPC) in Gout, Rheumatic Fever and Rheumatoid Arthritis. Am. J. M. Sc. **222:** 523 (Nov.), 1951.

The effect of 3-hydroxy-2-phenylcinchoninic acid (HPC) was observed by the authors in four patients with gout, six with rheumatic fever, and 10 with rheumatoid arthritis. This agent was used in doses ranging from 20 to 40 mg. per kilogram of body

weight per day for periods of 5 to 35 days. The four patients with gouty arthritis showed marked subjective and objective improvement, three within 24 hours of the first dose. In three of these patients the response was as satisfactory as that obtained with colchicine. Of the 10 patients with rheumatoid arthritis, two were markedly improved, five were somewhat improved and two showed no improvement. One patient became worse during treatment. The six patients with rheumatic fever responded to HPC with a return of temperature to normal within 12 to 48 hours, and subsidence of joint manifestations within two to five days. The sedimentation rates did not improve.

The toxic effects encountered during treatment with HPC included urinary frequency (nine cases), dysuria (three cases), nocturia (one case), nitrogen retention with impaired renal function (one case), nausea (one case), vomiting (one case), diarrhea (eight cases), cutaneous photosensitivity (three cases), neuropathy (one case), and bradycardia (one case). One or more toxic reactions were noted in 16 of the 20 patients treated.

The antirheumatic effect of HPC appears to be no greater than that of salicylates in rheumatic fever and rheumatoid arthritis. In gout, it may be as effective as colchicine.

SHUMAN

Drill, V., and Bristol, W.: Comparison of Water and Saline Hydration on Diuretic Action of Sympathomimetic Agents. Endocrinology **49:** 589 (Nov.), 1951.

The diuretic effect of norepinephrine, epinephrine, ephedrine and Privine were compared in normal rats hydrated with water, and in rats hydrated with 0.85 per cent sodium chloride, which normally produces a delayed urine excretion. Studies were also made of the chloruretic effect of these amines. The method of Ham and Landis was used, the amines being administered subcutaneously before the second dose of water.

Epinephrine and norepinephrine produced a marked diuretic effect in animals hydrated with water or 0.85 per cent sodium chloride, with a prompt onset of diuresis. Privine produced a moderate diuresis with both hydrating solutions, but ephedrine had no diuretic effect in either series. Epinephrine, norepinephrine, and Privine showed a definite chloruretic effect in animals hydrated with water, but not in the animals hydrated with 0.85 per cent sodium chloride. Ephedrine showed no chloruretic effect. The possible relationship of the adrenal medulla to diuresis is discussed.

CORTELL

Black, D. A. K., and Thomson, A. E.: Day-to-day Changes in Sodium and Water Output with and without Posterior Pituitary Extract. Clin. Sc. **10:** 511 (Nov.), 1951.

Two sets of experiments were done on two normal subjects, the duration of the experiments varying from 10 to 16 days. There were strikingly large variations in sodium output and urinary volume from day to day, whereas creatinine excretion occurred at a relatively stable rate. Potassium output was less variable than sodium, and daily chloride output was closely correlated with sodium. Close correlation was found between daily urine volume and sodium output. Posterior pituitary extract exerted no important effects upon sodium and potassium excretion.

The authors suggest that although sodium concentration in extracellular fluid is affected by antidiuretic hormone, the effect is through variations in water output. However, changes in sodium balance are brought about by adrenal cortical activity. Clinical support for this view is found in the absence of changes in sodium balance in diabetes insipidus in contrast to the severe depletion of Addison's disease. Excessive sodium loss does not occur in water diuresis, but is present in osmotic diuresis as in the glycosuria of severe diabetes mellitus.

ENSELBERG

Beck, H. D.: The Treatment of Arteriosclerotic Disturbances of the Circulation with Dibenamine. Deutsch. Med. Wchnschr. **44:** 1369 (Nov.), 1951.

Thirty patients with signs of impaired circulation of the extremities (22 on arteriosclerotic basis, seven with Buerger's disease and one case of Raynaud's disease) were treated with intravenous infusions of Dibenamine in a dose of 5 mg. per kilogram body weight, repeated four to five times in three-day intervals.

Clinical improvement, persisting in some cases for more than a year, was seen in patients with arteriosclerotic lesions if the latter were localized below the origin of the deep femoral artery. In cases with complete obstruction of the femoral artery (lack of filling in arteriograms) and in all cases of Buerger's disease, the treatment failed to improve the symptoms like intermittent claudication in spite of considerable increase of the skin temperature in the affected extremities. Striking and long standing improvement with disappearance of necrotic skin lesions was effected in the single case of Raynaud's disease, treated by this method.

PICK

Drury, A.: The Effect of Epinephrine and Insulin on the Plasma Potassium Level. Endocrinology **49:** 663 (Nov.), 1951.

The administration of epinephrine subcutaneously to normal, adrenalectomized, adrenal enucleated and hypophysectomized rats resulted in a significant lowering of the plasma potassium level at the end of 60 minutes, with a return to normal at the end of 120 minutes. Insulin caused a fall in plasma potassium level only in normal rats after 60 min-

utes, but had no effect on the plasma potassium in adrenalectomized or adrenal enucleated rats. Since epinephrine lowered the plasma potassium in adrenalectomized and hypophysectomized rats as well as intact rats, it is concluded that this effect of epinephrine is not mediated through the adrenal cortex nor through the pituitary-adrenocortical axis.

Hyperglycemia produced by the administration of large amounts of glucose by mouth to intact rats had no significant effect on the plasma potassium level, indicating that the action of epinephrine was not the result of its hyperglycemic action. Hypoglycemia induced by insulin did not prevent the decrease in plasma potassium level caused by epinephrine.

The evidence presented here indicates that epinephrine as such has an integral role in potassium homeostasis, whereas insulin appears to act by "reflex" stimulation of the adrenal medulla, since it is ineffective in adrenalectomized and adrenal enucleated rats.

CORTELL

Weston, R. E., Grossman, J., Lehman, I., Ullman, T. D., Halperin, J. P., and Leiter, L.: Renal Extraction and Excretion of Mercury in Man Following Intravenously Administered Mercurial Diuretics. J. Clin. Investigation **30:** 1221 (Nov.), 1951.

The mechanisms by which mercury is removed from the plasma was studied in six patients by simultaneous measurements of renal hemodynamics and blood and urine concentrations of mercury and electrolytes. Analysis of the data shows that the usual concept of "clearance" cannot be applied to the renal excretion of mercury, since there was evidence of fixation of mercury by renal tissue and subsequent release. Despite the rapid excretion of mercury in the urine during the early part of the collection period, mercury was removed by the kidneys in significantly greater amounts than that eliminated. After two hours, when the arteriovenous difference was no longer measurable, a considerable amount of mercury appeared in the urine.

WAIFE

PHYSICAL SIGNS

Rueger, M. J.: Blood Pressure Variations in the Two Arms. Ann. Int. Med. **35:** 1023 (Nov.), 1951.

There can be a significant incidence of variation in both the systolic and diastolic blood pressure in the two arms in patients with normal and abnormal cardiovascular systems. The difference may be of vital importance to an individual in the case of examination for life insurance, employment or military service. It is recommended that at the time of the first examination of any individual, the blood pressure be taken in both arms, and for follow-up studies one of these limbs should be selected for the estimation of the blood pressure.

The variation of the blood pressure in the two arms is probably due to a number of factors, one of which is differences in the caliber of the arteries of the two arms. Other causes may be external pressures on the vessels, atheromatous plaques and the state of contraction of the vessels.

WENDKOS

PHYSIOLOGY

Hoffman, W. K.: Relation of Atrial Inflow Rate to Intra-atrial Pressure Gradient during Ventricular Systole (Z-V gradient). Am. J. Physiol. **167:** 435 (Nov.), 1951.

It has been suggested that the gradient between the atrial pressure just before ventricular systole (Z pressure) and that pressure in the atrium at the second sound artefact (V pressure) should be altered by the rate of atrial inflow, during this period of ventricular systole when the right atrium is a closed chamber. Z-V gradients may be plotted as directional arrows connecting the Z-V points. These arrows are rotated clockwise by an increase in atrial inflow, counterclockwise by decreased in flow. The increase in inflow is only reflected accurately by the change in Z-V gradient in two successive cycles with relatively constant Z points. Clear cut changes in the Z-V gradient do not take place after the first cycle because after this the Z point rises more rapidly and causes a clockwise rotation in the Z-V gradient although the atrial inflow is still increasing.

OPPENHEIMER

Turner, L. B., and Grollman, A.: Role of Adrenal in Pathogenesis of Experimental Renal Hypertension as Determined by a Study of the Bilaterally Adrenalectomized Nephrectomized Dog. Am. J. Physiol. **167:** 462 (Nov.), 1951.

By means of intermittent peritoneal lavage, bilaterally adrenalectomized, nephrectomized dogs survived for as long as 40 days without hormone therapy. These dogs became hypertensive. Postmortem findings in heart and vessels were like those in animals with nephrectomy alone. The authors conclude that the adrenals do not determine the development of hypertension. It is also pointed out that when judged by the findings in these experiments, adrenalectomy for the treatment of hypertension seems irrational.

OPPENHEIMER

Heymans, C., and Delaunois, A. L.: Fundamental Role of the Tone and Resistance to Stretch of the Carotid Sinus Arteries in the Reflex Regulation of Blood Pressure. Science **114:** 546 (Nov. 23), 1951.

The tone and resistance to stretch of the arterial wall in the carotid sinus area, where the pressoreceptors are located, are the fundamental factors for the reflex automatic regulation of the systemic

arterial pressure according to previous experiments by these workers. In this report, a segment of the common carotid artery was immersed in Tyrode solution and pure *l*-epinephrine or *l*-norepinephrine bitartrate was applied in dilute concentrations.

Under the conditions of this experiment, *l*-norepinephrine and *l*-epinephrine applied to the carotid sinus induced a contraction of the arterial wall of this area. This contraction provoked the stimulation of the carotid sinus pressoreceptors, and, thus, the reflex fall of the systemic arterial pressure previously observed. These findings re-emphasized the importance of the tone and resistance to stretch of the arterial wall and the carotid sinus area in the regulation of blood pressure.

WAIFE

RHEUMATIC FEVER

Dorfman, A., Smull, K., Bergenstall, D. M., Howard, R., Muller, R., Oleson, D., and Senz, E.: The Effect of ACTH on Rheumatic Fever. Pediatrics **8**: 603 (Nov.), 1951.

Twenty-one patients with rheumatic fever, ranging in age from 3½ to 15 years, were treated with adrenocorticotropic hormone (ACTH) and one with cortisone. All cases received 250,000 units of oral penicillin once each day. Sodium chloride was restricted in those with severe heart disease. During therapy, 2.4 Gm. of potassium chloride was given to most of the patients. The ACTH was administered intramuscularly in equally divided doses every six hours. The dosage was begun at 80 mg. per day, after two days decreased to 40 mg. per day, and decreased further shortly before the therapy was completed. The duration of drug therapy ranged from four to six weeks in the majority of the patients.

Prior to therapy 19 showed a significant elevation in temperature. During therapy only three showed no definite diminution of fever. These had pancarditis and died while undergoing treatment. Nodules were present in three, disappeared during therapy and did not reappear after the withdrawal of the drug. Eighteen patients had a significant decrease in their sedimentation rates. A pericardial friction rub was present in 10 patients prior to therapy and disappeared in all (seven) except in those patients who died. A resting pulse rate, which was over 100 in all the patients, disappeared and returned to normal during therapy except in the fatal cases. In six patients there was aortic regurgitation and three exhibited increased evidence of regurgitation during the course of treatment.

In general, the various murmurs showed no significant change. There was a decrease in the heart size in 8 per cent of the 17 patients who demonstrated cardiac enlargement. Congestive heart failure which was present in 13 cases decreased in 10 cases under therapy. Ten patients showed a prolongation of the P-R interval which returned to normal in four. In almost all of the patients there was a definite reactivation on withdrawal of the drug. The therapy did not prevent death due to acute rheumatic pancarditis. There was no evidence to indicate that the treatment changes the incidence of late valvular deformities. The authors conclude that ACTH therapy represses the manifestations of active rheumatic fever, but state that there is no conclusive evidence that ACTH therapy alters the natural course of this disease.

MARGOLIES

ROENTGENOLOGY

Jackson, F.: The Radiology of Acute Pulmonary Edema. Brit. Heart J. **13**: 503 (Oct.), 1951.

The x-ray appearance of acute pulmonary edema is described in 20 subjects. Ten hypertensives are included in this group; two were malignant, four nephritic and four without renal involvement. In the remaining cases, one had normal pressure and a large heart, three had aortic regurgitation and six had mitral stenosis.

The lungs show homogeneous or uneven confluent opacities that blot out the lung vessels or even parts of the heart. They extend bilaterally, sometimes to a greater extent on the right side, for various distances into the lung fields and usually end below the apices, above the costophrenic angles and just before they reach the lateral chest wall. A fainter type appears as pin-head stippled densities. Another type is characterized by blurred, branched finger-like processes. The diaphragm is not elevated. The superior vena cava is not dilated.

The lesions may disappear with remarkable rapidity. Hilar congestion may remain. The lesions are probably due to fluid collections in the air spaces of the lung. They are not related to uremia.

SOLOFF

Wittenborg, M. H., Neuhauser, E. B. D., and Sprunt, W. H.: Roentgenographic Findings in Congenital Tricuspid Atresia with Hypoplasia of the Right Ventricle. Am. J. Roentgenol. **66**: 72 (Nov.), 1951.

The authors discuss the roentgen findings in 11 patients with congenital tricuspid atresia. Only two of these presented the characteristic findings of left ventricular enlargement: concavity of the left middle segment denoting a narrowed pulmonary artery trunk; straightening or concavity of the right contour in the postero-anterior view and the anterior contour in the left anterior oblique position; diminished prominence of the peripheral pulmonary vascular markings; direct evidence of reduced pulmonary blood flow.

Four of the others occurred with isolated dextrocardia (without visceral transposition), all with the aortic arch descending on the left or "reversed" side. In these four as well as the other five cases in which the left ventricle was on the normal or left

side, it was very difficult to determine whether the left lower contour rounding was due to left or to right ventricular enlargement, presenting a "coeur en sabot" appearance. In the nontypical cases, right auricular enlargement apparently obscured the absence or hypoplasia of the right ventricle, often simulating the silhouette in tetralogy of Fallot.

Survival in tricuspid atresia requires an atrial septal defect shunting blood from right to left, also a patent ductus arteriosus for oxygenation of this shunted blood. The authors make a point of the size of the atrial septal defect, and indicate that the right auricle must enlarge more with small than with larger atrial defects. The size of the ductus arteriosus and the presence or absence of a functioning interventricular septal defect are other factors in determining pulmonary blood flow, life expectancy and operability.

Electrocardiographic left axis deviation is not always present. Left ventricular preponderance or absence of evidence for right ventricular hypertrophy is almost as conclusive.

SCHWEDEL

Segers, M.: Impression of the Esophagus due to Patent Ductus Arteriosus. Arch. d. mal. du coeur **44:** 1037 (Nov.), 1951.

In a 14 years old boy with typical acoustic and radiologic signs of a patent ductus arteriosus, an unusual indentation of the esophagogram was found at repeated examinations. It was located 1.5 cm. below the normal aortic impression and showed distinct pulsations, synchronous with those of the aorta. Location of the indentation on the anterior aspect of the esophagus ruled out the presence of an anomalous origin of the left subclavian artery with crossing from right to left. The author stresses the rarity of this observation which, however, might occasionally be helpful in establishing the diagnosis of a patent ductus arteriosus in the absence of other typical clinical features.

PICK

Witz, J. and Schmidt, C.: Angiocardiographic Diagnosis of a Prominent Pulmonary Segment. Arch. d. mal. du coeur **44:** 1019 (Nov.), 1951.

The authors discuss the differential diagnosis of various conditions with the radiologic sign of a prominent left middle segment of the heart shadow. Angiocardiography was performed without accident in 22 such cases, and, according to the findings, the cases could be divided into two main groups.

The first group included cases with symptomatic dilatation of the pulmonary artery, either on a congenital basis (patent ductus arteriosus, interauricular septal defect, Eisenmenger's complex, pulmonary stenosis), or acquired (primary and secondary pulmonary sclerosis, mitral stenosis, syphilitic pulmonary arteritis). The second group consisted of cases with idiopathic dilatation of the pulmonary artery.

The characteristic angiocardiographic sign of a patent ductus arteriosus is re-injection of the pulmonary artery following left ventricular filling. The ductus itself can be visualized only exceptionally, and an invagination of the inferior part of the aortic segment as described by others was never observed by the authors. A typical radiologic sign of interatrial septal defect is the marked hilar dance, and, at angiocardiography, reinjection of the pulmonary artery while the aortic shadow is only poorly outlined. Pulsations of a dextroposed aorta in Eisenmenger's complex can occasionally be mistaken for hilar pulsations. In pulmonary stenosis, angiocardiography may reveal dilation of the pulmonary artery below or above the constriction. The latter is found in about 50 per cent of isolated pulmonary stenosis, but never if the pulmonary lesion is associated with other congenital anomalies. "Idiopathic" dilatation of the pulmonary artery found in the angiocardiogram of an adult always suggests that the enlargement of the pulmonary trunk may have developed secondary to pulmonary hypertension.

PICK

SURGERY OF HEART AND VASCULAR SYSTEM

Lam, C. R., and Aram, H. H.: Resection of the Descending Thoracic Aorta for Aneurysm: A Report of the Use of a Homograft in a Case and an Experimental Study. Ann. Surg. **134:** 743 (Oct.), 1951.

The authors described a case of a patient with an aneurysm of the descending aorta, about the size of a large grapefruit, which was treated by the use of a homograft removed from a cadaver 10 hours after death. The aorta was transected proximally and distally as close to the aneurysm as possible, and a lucite tube, over which the graft had been placed, was inserted into the upper and lower ends of the vessel. Then the proximal end of the graft was attached to the aorta, followed by the same procedure in the lower end. When the anastomosis at the distal portion was two-thirds finished, clamps were reapplied so as to permit the lucite tube to be extracted, and then the opening was closed completely. The aneurysmal sac was not removed.

The postoperative course was uneventful and the patient left the hospital 42 days after surgery was performed. However, he was readmitted 44 days later because of hemoptysis and cough, and died the same day. On postmortem examination, a large mediastinal abscess was found in the vicinity of the old aneurysm. Histologic examination of the aorta revealed firm fibrous union of the graft at the proximal anastomisis, while the distal one presented partial separation of the edges, but with sufficient adventitial scarring to prevent hemorrhage.

ABRAMSON

Kantrowitz, A., Hurwitt, E., and Kantrowitz, A.: Experimental Artificial Left Heart for Exposure of the Mitral Area. Arch. Surg. **63:** 604 (Nov.), 1951.

This experimental method, for use in mitral surgery, uses the animal's own lungs for aeration of the blood in the system. Cannulas are placed in a cephalod direction in both femoral arteries, other cannulas are passed through the left auricular appendage and chamber of the left auricle into the openings of the left pulmonary veins, and then the artificial system previously filled with blood from a donor animal is started. The blood coming from the right lung is allowed to pass through the left side of the animal's heart, while that coming from the left lung is collected by the cannulas and delivered via the artificial system and the femoral arteries to the animal's aorta. When the system appears to be working properly, the right pulmonary artery is occluded so that all the blood is shunted through the left lung and the artificial system. At this point, the mitral valve is in a bloodless field and can be subjected to surgery.

To discontinue the artificial and restore the normal circulation, the tourniquet around the right pulmonary artery is gradually released, so as to allow blood again to pass through the right lung and return to the animal's left auricle. The cannulas in the left pulmonary veins are withdrawn into the left auricle and removed through the appendage, which is then ligated.

After the technic was established, cats were still alive over 36 hours after termination of the procedure. It was also tried on dogs with some modifications.

ABRAMSON

O'Neill, T. J. E., Glover, R. P., and Bailey, C. P.: Observations on the Surgical Treatment of Mitral Stenosis by Commissurotomy. J. A. M. A. **147:** 1032 (Nov. 10), 1951.

The authors operated on 214 patients from June 10, 1948 through May 1951. In more than 100 of these patients, at least a six-month follow-up is available.

The procedure is aimed primarily at enlarging the stenotic orifice so as to allow greater transfer of blood from the left atrium to the left ventricle. This must be accomplished without any significant production of regurgitation. The use of the knife rather than the so-called finger fracture of the commissures is advised.

Cases of mitral stenosis are divided into five stages. Stage I (asymptomatic) cases are obviously not in need of operative intervention. Stage II (statically incapacitating) cases are the best group for surgical intervention. Stage III (progressively incapacitating) cases may have passed the optimum time for operation but still constitute favorable candidates. Stage IV (terminally incapacitating) cases should be operated upon although it is to be realized that this is the least favorable stage. The irretrievable, or stage V, cases are not considered operable.

Results in the 214 cases were excellent in 89, improved in 70, unimproved in 29, and death for 26 from various causes. Thus 74 per cent of the patients have either improved or are now in excellent condition. The 13 per cent unimproved are generally in no worse state than they had been preoperatively, according to the authors. Total operative survival rate is 89.8 per cent.

KITCHELL

THROMBOEMBOLIC PHENOMENA

Johnson, J., and Kirby, C. K.: The Surgical Treatment of Ventricular Fibrillation. Ann. Surg. **134:** 672 (Oct.), 1951.

The authors reported on the treatment of 10 patients who developed ventricular fibrillation during the course of an operation. Four recovered completely; six died. In the former, resuscitative measures were begun within four minutes of the onset of ventricular fibrillation. In the others there was a longer delay. Seven of the patients had cardiac arrest when the heart was first exposed, the ventricular fibrillation appearing after the heart had been massaged for several minutes.

According to the authors, certain measures are necessary in order to treat ventricular fibrillation. Cardiac massage and adequate respiration, produced by artificial ventilation of the lungs, must be established within about four minutes, for otherwise the cerebral tissue will be irreparably damaged by the anoxia. The rate of cardiac compression should be 80 to 120 times per minute. The venous return to the heart should be supplemented by moderately rapid intravenous administration of crystalloid solutions and blood. Procaine or Pronestyl should be administered intravenously. Finally when the heart demonstrates an improved coronary circulation, it should be exposed to the electric defibrillator. The electrodes are pressed firmly against the anterior and posterior walls of the myocardium, and three shocks of less than one second's duration are thrown into the heart at intervals of one second.

ABRAMSON

AMERICAN HEART ASSOCIATION, INC.

1775 Broadway, New York 19, N. Y.

Telephone Plaza 7-2045

MANUSCRIPTS FOR "CIRCULATION RESEARCH"

Manuscripts for the Association's new bimonthly scientific journal, Circulation Research which will begin publication next January, will be considered after October 1. The new journal will be devoted exclusively to basic research on the cardiovascular system from various disciplines, including biology, biochemistry, biophysics, morphology, pathology, physiology, and pharmacology. Clinical research which contributes to an understanding of basic problems will be included.

Circulation, which continues as a monthly publication, will concentrate more fully on applied research and clinical problems of interest to the clinician in caring for his patients.

In addition to regular papers, Circulation Research will include preliminary reports of current research advances considered significant by the editors. Such contributions should not exceed 500 words.

Material must be restricted to new research material which has not been or will not be published elsewhere.

Further information regarding editorial requirements may be obtained by writing to Dr. Carl J. Wiggers, Editor, Circulation Research, 2109 Adelbert Rd., Cleveland 6, Ohio.

SUBSCRIPTION RATES

Subscription rates for the bimonthly journal Circulation Research have been set below publication cost to encourage the widest possible readership. The Association will assume the difference as part of its professional education program. Research Journal Membership subscriptions, available through the Association, include the monthly bulletin, *Modern Concepts of Cardiovascular Disease*, and admission to the Association's annual Scientific Sessions.

The annual rates are as follows:

Research Journal Membership subscription $9.50
(In Canada and foreign countries ..... $10.50)

Direct subscription to Circulation Research is available from the publisher, Grune & Stratton, Inc., at $7.50 per year, but does not include Association membership privileges.

Combined Membership Subscription, Circulation and Circulation Research $19.50
(In Canada and foreign countries ..... $21.50)

Special Rate

Persons engaged in full-time research work may, upon application, obtain for their own personal use a subscription to Circulation Research for $6.00, or a Research Journal Membership Subscription, including Association membership privileges, for $8.00.

ANNUAL MEETING AND SCIENTIFIC SESSIONS

The Twenty-Ninth Annual Meeting and the Twenty-Sixth Scientific Sessions of the American Heart Association will be held at the Hotel Chelsea in Atlantic City, N. J., April 8–12, 1953, immediately preceding the annual meeting of the American College of Physicians. All those desiring to attend should make room reservations directly with hotels in Atlantic City at the earliest possible date. The Scientific Sessions will be held on Thursday, Friday, Saturday, and Sunday, April 9, 10, 11, and 12.

PAPERS FOR SCIENTIFIC SESSIONS

All those desiring to present papers at the Association's Scientific Sessions should submit abstracts in triplicate of the proposed presentation to Dr. André Cournand, Chairman of the

Program Committee, % American Heart Association, 44 East 23rd Street, New York 10, N. Y. not later than January 1, 1953. Abstracts should not be longer than 300 words and must contain in summary form a specific statement of the results obtained or conclusions reached (not merely a statement that results or conclusions will be presented or discussed at the meeting).

ASSOCIATION FELLOWSHIPS AND GRANTS

Applications for Research Fellowships and Established Investigatorships for the 1953–54 fiscal year will be accepted by the Association up to September 15, 1952. Applications for research grants-in-aid may be filed up to December 1, 1952. Information and forms may be obtained from the Association's Medical Director.

Applications will be reviewed by the Research Committee of the Scientific Council. Awards will be made from funds raised in the 1952 Heart Fund campaign.

Research Fellowships are granted for a one-year period, and range from $3,500 to $5,500. Established Investigatorships may be extended annually for a five-year period, and range from $6,000 to $9,000. Grants-in-aid, including grants for basic research, are awarded in varying amounts usually not exceeding $10,000, and the period covered is variable, usually depending on the particular program of study.

NEW ADDRESS

Communications after September 20 should be directed to the Association's new address: 44 E. 23rd Street, New York 10, N. Y. Phone, Gramercy 7-9170.

HOWARD W. BLAKESLEE AWARD

An annual award to be known as the Howard W. Blakeslee Award has been established by the Association to encourage high standards of medical reporting in all media on developments in the field of heart and blood vessel diseases. The award was named in honor of Mr. Blakeslee, who recently died of heart disease, because of his outstanding contributions toward raising the level of scientific reporting.

Mr. Blakeslee was Science Editor of the Associated Press and a founder of the National Association of Science Writers which has officially endorsed the award.

As approved by the American Heart Association's Board of Directors, the Howard W. Blakeslee Award will be presented annually to the individual whose creative efforts in any medium of mass communication—including press, magazines, radio, television, films and books—contribute most to public understanding of the cardiovascular diseases. Describing the Association's purposes in creating the Award, Dr. Irving S. Wright, President, said: "The past few years have witnessed a tremendous growth of public interest in the medical sciences as the nation has become increasingly health conscious. Science reporters in the press, as well as other media, are shouldering an enormous burden in attempting to fill the public demand for knowledge and information. They have a serious responsibility for faithfully and accurately reporting medical developments to the satisfaction of the scientist and physician, as well as for promoting better understanding on the part of the general public. In the broad field of heart and blood vessel diseases, great advances are being made, and it is an important objective of the American Heart Association to foster good working relations between science reporters and the medical profession so that the needs and interests of the public will best be served."

LIFE INSURANCE MEDICAL RESEARCH FUND

Applications for awards available July 1, 1953, will be received by the Life Insurance Medical Research Fund as follows: (1) Postdoctoral research fellowships, until October 31, 1952. Preference is given to those who wish to work on cardiovascular function and disease or related fundamental problems. Stipends vary from $3,300 to $4,500. (2) Grants to institutions in aid of research on cardiovascular problems, until November 15, 1952. Support is available for physiologic, biochemical, and other basic research on cardiovascular problems as well as for clinical investigation in this field. Further information and application blanks

may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103rd Street, New York 29, N. Y.

FULBRIGHT AWARDS

Fulbright Awards are available for university lecturing and postdoctoral level research in Europe and the Near East for 1953–54. Applications must be made by October 15, 1952. The Fulbright Grants were established by the Seventy-ninth Congress as part of the educational exchange program to promote better understanding of the United States in other countries and to increase mutual understanding between Americans and peoples of other nations. Application forms and additional information may be obtained from the Conference Board of Associated Research Councils, Committee on International Exchange of Persons, 2101 Constitution Avenue, N.W., Washington 25, D. C.

NEW AFFILIATE

The Albany County Heart Association in New York State has been accepted by the Board as a direct affiliate of the American Heart Association.

POSTGRADUATE SYMPOSIUM

The San Francisco Heart Association will present its Annual Postgraduate Symposium on Heart Disease October 22, 23, and 24, 1952, at the St. Francis Hotel. Guest speakers will be Drs. C. Sidney Burwell of the Harvard University School of Medicine; Julius H. Comroe, Jr., of the Graduate School of Medicine, University of Pennsylvania; and Hans H. Hecht of the College of Medicine, University of Utah. The Symposium, which usually attracts physicians from neighboring states, will include a course in unipolar electrocardiography, a session on Childhood Heart Disease planned for pediatricians, and clinical demonstrations. Further information may be obtained from the San Francisco Heart Association, 604 Mission Street, San Francisco 5, Calif.

NEW COMMITTEES

Charles E. Kossmann, M.D., New York City, has been appointed Chairman of the new Committee on Electrocardiography. A Committee on Ballistocardiography also has been formed, under the Chairmanship of Isaac D. Starr, M.D., Philadelphia.

EDUCATIONAL MATERIALS

The American Heart Association, through its year-round professional and lay educational program, offers manuals, booklets, films and radio features of interest to physicians as well as the general public. Listed below are some of the more recent materials distributed by the Association which may help the physician in professional educational activities with which he may be connected, in dealing with the patient, or in participating in community action. Complete lists of materials available and further information may be obtained through the local heart association affiliate, or the National Office, unless otherwise noted.

Heart Models

Ten new latex rubber models of normal and abnormal hearts may be purchased from the Association as an aid in undergraduate and postgraduate education and for demonstrating heart conditions to patients and lay groups. They are especially useful in teaching fluoroscopy. These life-sized hearts were prepared by Abram Belskie, medical sculptor at New York Medical College. Outlines of the main coronary blood vessels and the reflections of the pericardium are shown on the surface. The heart models may be obtained singly at $22.50 with a diaphragm base, and at $16.50 without the base. The complete set of 10, all in natural latex rubber, cost $150.00 with one base. Instructions for coloring are sent with the models.

New Booklets

Diseases of the Heart and Blood Vessels, Facts and Figures, a 16-page handbook, with 12 graphic charts to highlight the answers to questions most often asked. Information covers incidence, disability, importance of sex and race, seasonal influences, and the most serious forms.

Be Smart, Protect Your Heart, a series of cartoon-illustrated health messages written by five former presidents of the American Heart Association, Drs. Howard B. Sprague, Tinsley R. Harrison, Louis N. Katz, Paul D. White, and A. R. Barnes. For distribution to patients and for use in community health-education programs.

Man to Man, a reassuring message on heart disease, written in popular style. Suggested for dis-

tribution by physicians to cardiac patients and their families.

The Work Classification Unit, a practical handbook prepared by the staff of Bellevue Hospital's Work Classification Unit, and published by the Association. It contains specific suggestions for setting up and operating a unit, and is particularly helpful for physicians, medical social workers and vocational counsellors concerned with employment problems of cardiacs.

Radio Transcriptions

Heart of America, a series of thirteen 15-minute radio transcriptions, now in production under the joint sponsorship of the Bureau of Health Education of the American Medical Association and the American Heart Association. Each script will feature a dramatic story of one aspect of cardiovascular disease, followed by a discussion by a leading cardiologist. These will be available through state and local medical societies, or Dr. W. W. Bauer, director of Health Education for the A.M.A.

The Human Heart, a series of eight 15-minute transcribed stories of people who learned to live with heart disease, featuring leading entertainment personalities. Each script records a statement by such leading medical authorities as Drs. Louis N. Katz, Paul D. White, Irvine H. Page, Robert E. Gross, T. Duckett Jones, C. J. Van Slyke, and Janet Baldwin. Address inquiries and orders to Communications Materials Center, Columbia University Press, 413 West 117th Street, New York 27, N. Y.

Revisions

Recommendations for Human Blood Pressure Determinations by Sphygmomanometers, a complete revision of the booklet, *Standardization of Blood Pressure Readings*. In addition to its distribution by the Association, it is being included with each sphygmomanometer shipped by three leading manufacturers of these instruments.

The Classification of Patients with Diseases of the Heart, (Wall Chart). A guide for recording more precisely the functional capacity and therapeutic classification of a cardiac patient. (Prepared and revised by New York Heart Association.)

Heart Disease Caused by Coronary Arteriosclerosis, by Paul D. White, M.D.; and *High Blood Pressure*, by E. V. Allen, M.D., have been revised and put in new format and larger type for easier use by physicians in discussions with patients and lay groups.

Films

Weight Reduction Through Diet, a 16 mm. full-color sound film, 15 minutes running time, produced by National Dairy Council. Documentary study of two controlled groups at Michigan State College over a four-month period. Film points up need for dieting under doctor's care for safety and proper results.

Care of the Cardiac Patient, a 16 mm. black and white sound film, 33 minutes running time, with film strip and teaching manual. Prepared by U. S. Office of Education. Especially suited to nurses' training. Demonstrates total care given a cardiac patient. Emphasis is put on the need for integration of all aspects of the patient's care.

Your Blood System, a 35 mm. film strip, silent, with 30 frames in full color. Produced by Curriculum Films. Designed especially for upper grade and high school classes in health, physiology, and biology. Also useful with lay study groups and as an introduction to talks on the heart and heart diseases.

Article Reprints

What the Heart Association Does for the Practicing Physician, by Howard B. Sprague, M.D., reprinted from GP, Journal of the Academy of General Practice. Outlines benefits of Heart Program.

How Should We Look at Heart Disease? by Paul D. White, M.D., reprinted from Religion and Health (February, 1952). Facts on heart disease, including information helpful to the clergy in giving spiritual counsel to heart patients.

Reduction

Proceedings of the First National Conference on Cardiovascular Diseases, the most comprehensive and up-to-date handbook on the subject, has been reduced from $1.75 to $1.25 a copy.

Special Publication

The Heart Bulletin, a bimonthly magazine, designed for the physician in general practice, reporting the latest advances in diagnosis and treatment of cardiovascular diseases. Paul D. White, M.D. is chairman of the Advisory Board, whose members were chosen in cooperation with the Association and the National Heart Institute. The bulletin does not duplicate any of the material issued by the Association. Published by the Medical Arts Foundation of Houston, a nonprofit service organization affiliated with the University of Texas.

CALENDAR

Aug. 31–Sept. 7: Inter-American Cardiological Congress, Buenos Aires, Argentina. Dr. Blas Moia, Secretary-General, Larrea 1132, Buenos Aires, Argentina.

Sept. 10–12: European Congress of Cardiology. University of London, Bloomsbury, W.C. 1, England. Dr. K. Shirley Smith, Secretary, 35 Wimpole Street, London, W.I., England.

Sept. 15–18: International Congress of Internal Medicine, Friends House, London, N.W. 1, England. Sir Harold Boldero, Secretary, 12 Pall Mall East, London, S.W. 1, England.

Sept. 20–28: American Congress of Industrial Medicine, Rio de Janeiro, Brazil. General Secretarial Office: Calle Arenales No. 981, Buenos Aires, Argentina.

Sept. 21–26: International Congress of Haematology, Mar del Plata, Argentina. Dr. Carlos Reussi, Secretary, Anchorena 1710, Buenos Aires, Argentina.

Sept. 27–Oct. 1: Inter-American Congress of Public Health, Havana, Cuba. Pan-American Sanitary Bureau, 2001 Connecticut Ave., Washington, D.C.

Oct. 3–4: European Society of Cardiovascular Surgery, Strasbourg, France. Sir James Learmonth, Dept. of Surgery, University New Buildings, Edinburgh 8, Scotland.

Oct. 12–16: World Medical Association, Athens, Greece. Dr. Louis H. Bauer, Secretary-General, 2 East 103rd Street, New York 29, N. Y.

Oct. 16–18: World Congress of Medicine, Montecatini, Italy. Secretariat: Corso Trieste 65, Rome, Italy.

Oct. 20–24: 80th Annual Meeting, American Public Health Association, Cleveland, Ohio. Reginald M. Atwater, M.D., Executive-Secretary, 1790 Broadway, New York 19, N. Y.

Nov. 10–12: Association of American Medical Colleges, 63rd Annual Meeting, Hotel Broadmoor, Colorado Springs, Col. Dean F. Smiley, M.D., Secretary, 185 North Wabash Avenue, Chicago 1, Ill.

AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

PROGRAM OF THE SIXTH ANNUAL MEETING TO BE HELD AT THE HOTEL KNICKERBOCKER IN CHICAGO, ILL., NOVEMBER 9–10, 1952

NOVEMBER 9, 1952

Morning

(G. Lyman Duff, Presiding)

8:15–9:15
Registration

9:15–9:20
Opening Session

9:20–9:35
1. The Effect of Heparin and Other Agents on the Cholesterol Partition and Lipoprotein Pattern. C. Moses, G. L. Rhodes, and C. Wray, Addison H. Gibson Laboratory, University of Pittsburgh, Pittsburgh, Pa.

9:35–9:40
Discussion

9:40–9:55
2. The Influence of Hormones on the Distribution of Lipoproteins in Plasma. D. P. Barr, E. M. Russ, and H. A. Eder, Department of Medicine, The New York Hospital, Cornell Medical Center, New York, N. Y.

9:55–10:00
Discussion

10:00–10:15
3. A New and Simple Technic for Detecting Disturbances in the Serum Lipid Pattern in Health and Disease. L. Horlick, Department of Pathology, Pathological Institute, McGill University, Montreal, Canada.

10:15–10:20
Discussion

10:20–10:35
4. Atherosclerosis: an in Vitro Study of the Nature of Atherogenesis. S. M. Evans, H. K. Ihrig, J. Means, W. Zeit, R. N. Hazelwood, and E. R. Haushalter, Departments of Medicine and Anatomy, Marquette University School of Medicine, and the Research Laboratories of Allis-Chalmers Manufacturing Co., Milwaukee, Wis.

10:35–10:40
Discussion

10:40–10:55
5. Foam-Cellular Lesions of the Aorta and Coronary Arteries of the Dog. L. L. Waters, Department of Pathology, Yale University School of Medicine, New Haven, Conn.

10:55–11:00
Discussion

11:00–11:15
6. Atherosclerosis of the Carotid Arteries. C. M. Fisher, J. E. Pritchard, and W. H. Mathews, The Montreal General Hospital, Montreal, Canada.

11:15–11:20
Discussion

11:20–11:35
7. The Interaction of "Heparin Active Factor" and Lipoproteins. A. V. Nichols, N. K. Freeman, B. Shore, and L. Rubin. Division of Medical Physics, Donner Laboratory and the Radiation Laboratory, University of California, Berkeley, Calif.

11:35–11:40
Discussion

11:40–11:55
8. Serum Cholesterol Values in Men on Habitually Different Diets—Italy, Spain, England and the United States. A. Keys, F. Fidanza, V. Scardi, G. Bergami, F. Vivanco, C. J. Diaz, and J. T. Anderson, Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minn.
11:55–12:00
Discussion

Afternoon

(Nelson W. Barker, Presiding)

2:00–2:30
Business Session*

2:30–2:45
9. The Effect of Brain Extract on Blood Cholesterol and the Serum Lipid Pattern. R. B. Gordon, S. Kraft, and R. J. Jones, Department of Medicine, University of Chicago, Chicago, Ill.
2:45–2:50
Discussion

2:50–3:05
10. Prevention of Hypercholesterolemia in the Rabbit: Successful Prevention of Cholesterol Atherosclerosis. Reduction of Blood Cholesterol in Man. O. J. Pollak, Dover, Del.
3:05–3:10
Discussion

3:10–3:25
11. Age-Conditioned Spontaneous Regression of Atherosclerosis in the Cholesterol-Fed Chick. S. Rodbard, R. Pick, C. Bolene-Williams, and L. N. Katz, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.
3:25–3:30
Discussion

3:30–3:45
12. Estrogen-Induced Regression of Coronary Atherosclerosis in Cholesterol-Fed Chicks. R. Pick, J. Stamler, S. Rodbard, and L. N. Katz, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.
3:45–3:50
Discussion

3:50–4:05
13. Endocrine Influences on Serum Lipoproteins and Atherogenesis in Cholesterol-Fed Chicks. J. Stamler, R. Pick, L. N. Katz, L. Lewis, and I. H. Page, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill., and Research Division, Cleveland Clinic Foundation, Cleveland, Ohio
4:05–4:10
Discussion

4:10–4:25
14. The Degree of Coronary Atherosclerosis in Castrated Women. J. H. Wuest, T. J. Dry, and J. E. Edwards, Division of Medicine and Section of Pathologic Anatomy, Mayo Clinic, Rochester, Minn.
4:25–4:30
Discussion

4:30–4:45
15. Digitonine Precipitation as a Method for Improving the Specificity of the Schultz Test. S. P. Kent, Department of Pathology, Medical College of Alabama and University of Alabama School of Dentistry, Birmingham, Ala.
4:45–4:50
Discussion

4:50–5:05
16. Plasma Heparin and Atherosclerosis. H. Engelberg, Los Angeles, Calif.
5:05–5:10
Discussion

7:30–10:30
Annual Dinner

* Will include discussion of paper #52.

NOVEMBER 10, 1952

Morning

(Russell L. Holman, Presiding)

9:00–9:15
Registration

9:15–9:20
Opening Session

9:20–9:35
17. The Distribution of the Vasa Vasorum of Arteries. C. A. Woerner, Department of Anatomy, University of Louisville, Louisville, Ky.

9:35–9:40
Discussion

9:40–9:55
18. Histochemical Studies of 5-Nucleotidase Activity in Human Aortas. I. Age and Regional Variations. C. H. Lupton, Jr., E. M. Etheridge, and J. F. A. McManus, Department of Pathology, School of Medicine, University of Virginia, Charlottesville, Va.

9:55–10:00
Discussion

10:00–10:15
19. Pathologic Changes of Endothelium Demonstrated by Impregnation with Silver Nitrate. R. Altschul, Department of Anatomy, University of Saskatchewan, Saskatoon, Canada.

10:15–10:20
Discussion

10:20–10:35
20. Surface Studies of the Early Development of Cholesterol Atherosclerosis in the Rabbit. E. V. Lautsch, G. C. McMillan, and G. L. Duff, Department of Pathology, Pathological Institute, McGill University, Montreal, Canada.

10:35–10:40
Discussion

10:40–10:55
21. Histochemical Studies of the Early Lesions of Cholesterol Atherosclerosis in the Rabbit. I. Klatzo, G. C. McMillan, and G. L. Duff, Department of Pathology, Pathological Institute, McGill University, Montreal, Canada.

10:55–11:00
Discussion

11:00–11:15
22. Factors Affecting the Distribution of Vascular Disease in Hypercholesterolemic Rabbits. G. M. Hass, F. B. Kelly, Jr., and C. B. Taylor, Rush Department of Pathology, The Presbyterian Hospital of the City of Chicago, Chicago, Ill.

11:15–11:20
Discussion

11:20–11:35
23. Arteriosclerosis in the Dog. A Comparison of Spontaneous and Experimental Lesions. S. Lindsay, and I. L. Chaikoff, University of California School of Medicine, San Francisco, Calif.

11:35–11:40
Discussion

11:40–11:55
24. Analysis of Aortic "Arteriosclerosis" in 300 Consecutive Autopsies. H. C. McGill, G. Peck, and R. L. Holman, Departments of Pathology, Louisiana State University School of Medicine, and Charity Hospital of Louisiana, New Orleans, La.

11:55–12:00
Discussion

Afternoon

(James C. Paterson, Presiding)

2:00–2:15
25. Relationships between the Levels of Dietary, Liver, and Serum Cholesterol and Hepatic Cholesterol Synthesis. I. D. Frantz, Jr., H. S. Schneider, and B. T. Hinkelman, Cardiovascular Re-

search Laboratory, Massachusetts General Hospital, and Harvard Medical School, Boston, Mass.

2:15–2:20
Discussion

2:20–2:35
26. Idiopathic Hypercholesteremia: Frequency in a Hospital Population and in the Families of Hypercholesteremic Index Patients. D. Adlersberg, S. R. Drachman, L. E. Schaefer, and A. G. Steinberg, Mount Sinai Hospital, New York, N. Y.

2:35–2:40
Discussion

2:40–2:55
27. Presenile Medial Calcinosis of the Arteries of the Extremities. N. W. Barker, H. L. Smith, and J. E. Edwards, Division of Medicine and Section of Pathologic Anatomy, Mayo Clinic, Rochester, Minn.

2:55–3:00
Discussion

3:00–3:15
28. Cation Content of the Aorta Wall in Renal and DCA Hypertension. L. Tobian, Jr., and J. Binion, Department of Biological Chemistry, Harvard University Medical School, Boston, Mass.

3:15–3:20
Discussion

3:20–3:35
29. Vascular Lesions Elicited by Renin in Nephrectomized Dogs. G. M. C. Masson, A. C. Corcoran, and I. H. Page, Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

3:35–3:40
Discussion

3:40–3:55
30. Vascular Response in Local and Systemic Circulation to Various Sympatholytic and Vasodilator Drugs Following Peripheral Cold Injury. B. Jablons, and A. H. Wolfson, Second Medical Division and Department of Pathology, Goldwater Memorial Hospital, New York, N. Y.

3:55–4:00
Discussion

4:00–4:15
31. The Effect of Aureomycin on Serum Lipids and Vascular Lesions in Cholesterol-Fed Rabbits. D. Nelson, R. Willheim, A. C. Ivy, and R. Altschul, Department of Clinical Science, University of Illinois, Chicago, Ill., and Department of Anatomy, University of Saskatchewan, Saskatoon, Saskatchewan, Canada.

4:15–4:20
Discussion

4:20–4:35
32. The Effect of Cortisone and ACTH on Experimental Cholesterol Atherosclerosis in Rabbits. E. Oppenheim, and M. Bruger, Department of Medicine, New York University Post-Graduate Medical School, New York, N. Y.

4:35–4:40
Discussion

4:40–5:00
Closing Session

TO BE READ BY TITLE

33. Peripheral Neurectomy for Pain in Obliterative Arterial Disease. A. Blain, III, and F. S. Gerbasi, Departments of Surgery, Alexander Blain Hospital, Detroit, and University of Michigan, Ann Arbor, Mich.

34. Genetic Studies on Coronary Atherosclerosis Developing after Age 60. E. P. Boas, and D. Adlersberg, Mount Sinai Hospital, New York, N. Y.

35. The Assay of Plasma Heparin, Using Anticoagulant Activity as a Measure of Heparin. L. Freeman, H. Engelberg, and A. Dudley, Cedars of Lebanon Hospital, Los Angeles, Calif.

36. The Effect of Choline on the Serum Cholesterol and Phospholipids in Patients with Coronary Artery Disease. S. U. Greenberg, and M. Bruger, Department of Medicine, New York University Post-Graduate Medical School, New York, N. Y.

37. Arteriosclerotic Popliteal Aneurysm: A Clinical and Follow-up Study. E. A. Hines, Jr., R. W. Gifford, Jr., and J. M. Janes, Division of Medicine and Section of Orthopedic Surgery, Mayo Clinic, Rochester, Minn.

38. The Ratio between Phospholipid and the Cholesterols of Blood as an Index of Human Atherosclerosis. R. S. Jackson, and C. F. Wilkinson, Jr., Department of Medicine, New York University Post-Graduate Medical School, New York, N. Y.

39. Effect of Testosterone and Chorionic Gonadotrophin on Estrogen-Induced Inhibition of Coronary Atherogenesis in Cholesterol-Fed Cockerels. L. N. Katz, J. Stamler, R. Pick, and S. Rodbard, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

40. In Vitro Lipoprotein Transformations. F. T. Lindgren, N. K. Freeman, and D. M. Graham, Division of Medical Physics, Donner Laboratory and the Radiation Laboratory, University of California, Berkeley, Calif.

41. The Results of Diet, Medicinal Agents and Emotional Disorders on Serum Phospholipid-Cholesterol Ratios in Coronary Atherosclerosis. L. M. Morrison, Los Angeles, Calif.

42. Studies on the Fate of C^{14}-Labeled Cholesterol and Its Oxidation Products after Intravenous Injection. E. H. Mosbach, W. Meyer, and F. E. Kendall, First Division (Columbia University), Goldwater Memorial Hospital, New York, N. Y.

43. Analytic Comparison of Cholesterol, Phospholipids and Ratios. J. W. Perry, E. W. Townsend, and P. B. Roen, Clinic for the Study of Arteriosclerosis, Hollywood Presbyterian Hospital, Los Angeles, Calif.

44. Influence of Gonadectomy on Cholesterol-Induced Aorta and Coronary Atherogenesis in Young Chicks. R. Pick, S. Rodbard, J. Stamler, and L. N. Katz, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

45. Prevention and Therapeutic Management of Atherosclerosis. P. B. Roen, E. W. Townsend, and J. W. Perry, Clinic for the Study of Arteriosclerosis, Hollywood Presbyterian Hospital, Los Angeles, Calif.

46. Cholesterol, Antilipfanogen and Fat Deposition. H. S. Simms, R. B. Best, and C. R. Harmison, Columbia University, College of Physicians and Surgeons, New York, N. Y.

47. Effects of Adrenal Steroid Compound F on Plasma Lipids and Atherogenesis in Cholesterol-Fed Chicks. J. Stamler, R. Pick, and L. N. Katz, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

48. The Effect of Estrogen on Serum Phospholipid. E. W. Townsend, J. W. Perry, and P. B. Roen, Clinic for the Study of Arteriosclerosis, Hollywood Presbyterian Hospital, Los Angeles, Calif.

49. A Comparison of the Chylomicron Index, Serum Total Cholesterol and Lipid Phosphorus as Indices of an "Atherosclerotic State." W. J. Zinn, and G. C. Griffith, Department of Medicine, University of Southern California School of Medicine, Los Angeles, Calif.

50. Studies on the Mechanism of the Regression of Experimentally Produced Arterial Lesions in Dogs. M. Bevans, L. L. Abell, and F. E. Kendall, First Division (Columbia University), Goldwater Memorial Hospital, New York, N. Y.

51. The Effect of Heparin and Placebo Therapy in Coronary Artery Disease. H. Miller, W. J. Zinn, and G. C. Griffith, Department of Medicine, University of Southern

California School of Medicine, Los Angeles, Calif.

12. Classification of Arteriopathies. J. B. Wolffe, Philadelphia, Pa., N. W. Barker, Rochester, Minn., A. C. Corcoran, Cleveland, Ohio, G. L. Duff, Montreal, Canada, and H. B. Sprague, Boston, Mass.; Nomenclature Committee of the American Society for the Study of Arteriosclerosis.

PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

ABSTRACTS

1. The Effect of Heparin and Other Agents on the Cholesterol Partition and Lipoprotein Pattern

Campbell Moses, Grace L. Rhodes, and Charlotte Wray

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Prior to and following the administration of intravenous and intramuscular heparin, Treburon, and the administration of inositol phosphatide, the cholesterol partition and S_f 12–20 pattern was determined. The effects of these agents will be described, and the implications so far as the therapy of atherosclerosis is concerned will be discussed. The effects of long-continued heparin administration in experimental atherosclerosis will be described.

2. The Influence of Hormones on the Distribution of Lipoproteins in Plasma

David P. Barr, Ella M. Russ, and Howard A. Eder

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In atherosclerotic men who have survived one or more myocardial infarctions, the administration of estrogens causes an increase in alpha lipoproteins and a corresponding diminution in beta lipoproteins. Usually, but not invariably, the concentration of cholesterol of the unfractionated plasma is decreased. Withdrawal of estrogens is followed at once by a substantial increase in the concentration of cholesterol in the plasma, by a diminution in alpha lipoproteins, and a corresponding increase in beta lipoproteins. The limiting factors and significance of these actions will be discussed. Data concerning the effects of androgenic hormones, thyrotoxin, cortisone and adrenotropic hormone upon the distribution of lipoproteins in plasma will be presented.

3. A New and Simple Technic for Detecting Disturbances in the Serum Lipid Pattern in Health and Disease

L. Horlick

Department of Pathology, Pathological Institute, McGill University, Montreal, Canada

Using the alpha toxin of *Clostridium welchii* which is a potent lecithinase, the lecithin of human serum is readily broken down to phosphocholine and a diglyceride. Coincident with the enzymatic hydrolysis of the lecithin, the serum becomes turbid. This is presumably due to the loss of the emulsifying action of lecithin on the hydrophobic lipids. Turbidity is measured by the Evelyn photoelectric colorimeter. The degree of turbidity is shown to be correlated with the level of the serum lipids, and most closely with the level of serum cholesterol. Using this technic it is possible to estimate accurately the serum cholesterol with as ittle as 0.2 ml. of serum within two hours. In addition, the amount of time taken for turbidity to appear is related to the cholesterol–lipid phosphorus ratio.

Using the criteria of early appearance of turbidity (high cholesterol–lipid phosphorus molar ratio), and high final turbidity reading (elevated serum cholesterol), it was possible to differentiate between groups of normal individuals and individuals with coronary disease who manifested disturbances in their lipid patterns. The simple test should serve as a rapid and economical screening method for detecting individuals with gross disturbances of the serum lipids resulting from a variety of diseases.

4. Atherosclerosis: an in Vitro Study of the Nature of Atherogenesis

S. M. Evans, H. K. Ihrig, J. Means, Walter Zeit, R. N. Hazelwood, and E. R. Haushalter

Departments of Medicine and Anatomy, Marquette University School of Medicine, and the Research Laboratories of Allis-Chalmers Manufacturing Co., Milwaukee, Wis.

An apparatus has been developed with which oxalated blood can be pulsated against strips of fresh human aorta obtained at autopsy. Grossly normal aortas from young adults are selected, and 6 to 14 single experiments may be run on each aorta.

Blood is selected from (a) "Test Sources," including recent cases of myocardial infarction, diabetics with vascular damage, etc., and (b) "Control Sources," including individuals with no apparent vascular disease. The sex and decade of life is the same in the two groups.

When an aorta is obtained, test source bloods and an equal number of control bloods are pulsated at 300/0 mm. Hg at a pulse rate of 80 per minute for 72 hours. The technical details involving apparatus and preparation of experiments are briefly presented.

At the end of the experiment, the aortic strips were studied by a variety of methods. A high order of significant differences between test and control source blood was observed only in the deposition of birefringent particles in the wall of the aortic strips. This phenomenon is evaluated both by polarized microscopy and by a photoelectric recording device which will be described. Results and their statistical analysis will be presented and the authors' tentative interpretation will be given.

5. Foam-Cellular Lesions of the Aorta and Coronary Arteries of the Dog

L. L. Waters

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Saline emulsions of egg-yolk are well tolerated when injected intravenously into dogs, and the injected lipids remain in the blood stream for relatively long periods. Injection of egg-yolk into normal dogs yielded lesions of the aorta but not of the coronary arteries. When allylamine injury of the coronary arteries was combined with injections of egg-yolk, large quantities of the injected fat localized selectively in the injured coronary artery segments as well as in the aorta. Foam-cellular intimal and medial lesions developed rapidly, often obliterating large vessels in two to three weeks. The fatty lesions are comparable morphologically to those following injections of methyl cellulose, and reproduce many of the features of early arteriosclerosis in man. The changes observed will be illustrated and the experimental method discussed as a tool for the study of the pathogenesis of arteriosclerosis.

6. Atherosclerosis of the Carotid Arteries

C. M. Fisher, J. E. Pritchard, and W. H. Mathews

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A special tendency for atherosclerosis to appear in the region of the carotid sinus has been reported on several occasions since 1900. Chiari found atherosclerosis to be as frequent, early and severe in the carotid sinus as in the abdominal aorta. The use of carotid arteriography (Moniz, 1937) led to the suspicion that occlusion of the carotid artery is frequent. About 100 cases so diagnosed have been reported, chiefly by neurosurgeons, and without pathologic confirmation. In 1942 Hultquist published a most extensive study of the carotid systems in 1400 autopsies. A detailed clinicopathologic correlation was not attempted.

This paper comprises a study of the carotid arteries in both routine autopsies and in cases labeled "ordinary strokes." In 18 months, more than 30 instances of unilateral or bilateral carotid occlusion have been found. As a cause of hemiplegia it ranks with embolism and hemorrhage. It is far more frequent than occlusion of the major vessels at the base of the brain. Unsuspected occlusion has been associated with "senile dementia" in several cases. Mural thrombus upon ulceration within the sinus can give rise to cerebral embolism.

The pathologic substrate for occlusion is usually atherosclerosis. The size of the plaque is striking. Atherosclerosis is often strictly limited to the sinus and the internal carotid artery between the sinus and the base of the skull never has any nodular atherosclerosis.

7. The Interaction of "Heparin Active Factor" and Lipoproteins

Alex V. Nichols, Norman K. Freeman, Bernard Shore, and Leonard Rubin

Division of Medical Physics, Donner Laboratory and the Radiation Laboratory, University of California, Berkeley, Calif.

The parenteral administration of heparin to humans and experimental animals has previously been shown to result in the production in vivo of an active factor capable of pro-

ducing marked serum lipoprotein transformations. The mechanism of action of this active factor might be better explored if satisfactory in vitro lipoprotein transformation systems were available and, secondly, if a means for readily assessing the concentration of the active principle were at hand. To these ends the interaction of egg lipoproteins (isolated from egg yolk by preparative ultracentrifugation) with the active principle has been studied.

If an aliquot of ordinary serum is incubated with a solution of egg yolk lipoprotein and subsequently diluted with a fixed volume of buffer solution (under constant pH, temperature, ionic strength), there results a turbid solution. This turbidity is apparently the result of aggregation and removal from solution of a fraction of the egg lipoprotein. If, however, the serum is replaced by an equal volume of plasma from an individual who has previously received heparin, the turbidity described above does not develop. It is possible to use the results of such incubation experiments to detect the presence of low concentrations of the heparin active factor and to approach its quantitative titration, using the turbidity change as an indicator.

It was observed that in order for heparin active factor to prevent the development of turbidity in the egg lipoprotein test, a prior incubation of the factor with lipid (either from serum lipoproteins or the egg lipoprotein itself) was essential. This suggested the possibility that fatty acid liberated during the incubation might be the immediate agent which prevented the turbidity development. This hypothesis was strengthened by the demonstration that sodium oleate itself, without prior incubation with lipid, and without heparin active factor, has the same effect in preventing turbidity development in the egg lipoprotein test as does the heparin active factor itself. It was then shown that the incubation of heparin active factor with egg yolk lipoprotein results in the liberation of titratable acid. By extraction with organic solvents and subsequent infra-red absorption analysis it has been possible to show that the titratable acidity is actually due to the liberation of fatty acid. It is apparent from these results that one phase at least of the action of heparin active factor upon lipoproteins may involve the liberation of fatty acids, presumably through a lipolytic mechanism.

8. Serum Cholesterol Values in Men on Habitually Different Diets—Italy, Spain, England and the United States

A. Keys, F. Fidanza, V. Scardi, G. Bergami, F. Vivanco, C. J. Diaz, and J. T. Anderson

Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minn.

9 The Effect of Brain Extract on Blood Cholesterol and the Serum Lipid Pattern

Robert B. Gordon, Sumner Kraft, and Richard J. Jones (introduced by Emmet B. Bay)

Department of Medicine, University of Chicago, Chicago, Ill.

It has been observed that the feeding of brain extracts or brain will cause the conversion of fecal cholesterol to coprosterol. Coprosterol, a reduction product of cholesterol, is not absorbed from the gastrointestinal tract. Coupling this fact with the knowledge that much of the endogenously produced cholesterol, as well as the ingested exogenous cholesterol, eventually enters the gastrointestinal tract, it was postulated that the feeding of brain extracts should make dietary cholesterol unavailable to the body and perhaps remove some endogenous cholesterol by affecting its conversion into coprosterol.

Experimentally, two groups of 12 cockerels were fed normal and 2 per cent cholesterol diets, respectively. Half of each group had its diet supplemented by a preparation of cholesterol-free brain extract. Analysis of the blood before and after feeding for two weeks showed significant differences between the lipid pattern of the treated groups and their controls. Total lipid, total cholesterol, phospholipid and the ultracentrifugal pattern were all determined in individual birds at the conclusion of the two-week period. The preparation of the extract and our results will be presented in detail with suggested implications in the control of atherogenesis.

10. Prevention of Hypercholesterolemia in the Rabbit: Successful Prevention of Cholesterol Atherosclerosis. Reduction of Blood Cholesterol in Man

O. J. Pollak

Dover, Del.

A certain organic compound, the nature of which will be disclosed, fed together with cholesterol to rabbits will prevent the hypercholesterolemia commonly resulting from cholesterol feeding to rabbits. This compound prevents selectively the intestinal resorption of cholesterol. The effect can be graded through variation of the ratio of the prophylactic agent and the ingested cholesterol. With this agent, a normal blood cholesterol level can be maintained in the rabbit, regardless of the amount of cholesterol fed. Prevention of hypercholesterolemia is, in the rabbit, tantamount to prevention of atherosclerosis caused by excessive cholesterol intake.

The same compound can be administered to man, without interference with the metabolism of any foodstuff other than cholesterol. With this agent, human blood cholesterol can be reduced to the basal level, that is, to the level maintained by endogenous cholesterol production. Cholesterol synthesis oscillates due to the complexity and variability of the human diet with its varying supply of acetates. The human body has a varying tendency or ability to compensate for deficiency of exogenous cholesterol through increased endogenous cholesterol synthesis. Because of these factors, control of the blood cholesterol through prevention of intestinal resorption of cholesterol, while possible, is not as simple in man as it is in the rabbit.

11. Age-Conditioned Spontaneous Regression of Atherosclerosis in the Cholesterol-Fed Chick

S. Rodbard, R. Pick, C. Bolene-Williams, and L. N. Katz

Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

Analysis of the natural history of atherosclerosis shows clearly that the state of development of the lesions fluctuates markedly during various periods in the life of the cholesterol-fed chick. At hatching no atherosclerosis is seen despite the fact that the chick has lived in a 2 per cent cholesterol environment for the entire embryonic period. In the succeeding period of about two months, cholesterol feeding of as much as 50 per cent of the diet resulted in no marked rise in plasma cholesterol level, or in the development of atheromatosis. In the experiment given below, 130 chicks were placed on a diet supplemented with 2 per cent cholesterol during the entire period of observation. With onset of puberty

(8 weeks), diffuse lipid infiltration and atherogenesis proceeds rapidly in coronary arteries, thoracic aorta, and other vessels throughout the body. At about 15 weeks of age, the diffuse infiltration regresses, and distinct localization of atherosclerotic plaques is observed. With sexual maturation (20 weeks) spontaneous regression of atherosclerosis begins, despite continued cholesterol feeding. Animals placed on a cholesterol diet at this time show retarded development of lesions. From 26 weeks up to 74 weeks the lesions regress, but pinpoint sclerosis on a thickened intima with occasional calcification remains. A rough correlation between the degree of development of the lesions and age-conditioned fluctuation in plasma cholesterol level may be observed. The type of vascular involvement, as well as susceptibility to atherosclerosis, is thus seen to depend in large measure on endogenous factors dependent on the age period of the animal.

12. Estrogen-Induced Regression of Coronary Atherosclerosis in Cholesterol-Fed Chicks

R. Pick, J. Stamler, S. Rodbard, and L. N. Katz

Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

Since it has been demonstrated that estrogen prophylactically inhibits cholesterol-induced coronary atherogenesis in chicks, a therapeutic-type study was undertaken to assess its ability to reverse previously induced coronary lesions.

Fifty cockerels were first fed a mash supplemented with 2 per cent cholesterol plus 5 per cent cottonseed oil (2 CO) for five weeks. Sacrifice of 10 birds confirmed the presence of aorta and coronary lesions in all. The remaining 40 chicks continued to receive 2 CO diet. In paired groups, the effect of a three- and a five-week course of estrogen (1 mg. daily) was then assayed. Despite continued cholesterol feeding, marked reversal of coronary lesions was effected by estrogen, in association with hormone-induced reduction of elevated plasma cholesterol/lipid phosphorus ratios toward normal levels. Both lipid and fibrotic components of coronary plaques regressed under the influence of estrogen. Concomitantly, aorta lesions exhibited no regression.

It is concluded: (1) Experimental cholesterol-induced coronary atherogenesis is a reversible process in cockerels. (2) Estrogens are effective against cholesterol-induced coronary atherogenesis in both prophylactic- and therapeutic-type studies.

13. Endocrine Influences on Serum Lipoproteins and Atherogenesis in Cholesterol-Fed Chicks

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Young growing cockerels normally exhibited a serum lipoprotein pattern on ultracentrifuge analysis (serums at density of 1.06 or 1.21) characterized by uniform presence of molecules of class S_f 3–8 ($-S_{1.21}$ 25–40). Molecules of the lower density classes were identifiable rarely or not at all.

Upon addition of 0.25 per cent cholesterol to the diet, lower density classes of lipoprotein molecules, particularly class S_f 10–20

molecules, rapidly appeared in serum, parallel with the minimal hypercholesterolemia induced by the regimen. Autopsy revealed: cholesterol-induced intensification of abdominal aorta lesions by the twentieth week of age; cholesterol-induced atherogenesis in the thoracic aorta by the thirty fifth week of age. None exhibited frank coronary atherosclerotic lesions.

Incorporation of progressively greater percentages (0.5 to 2 per cent) of cholesterol in the mash led to further marked alterations from normal beta-globulin lipoprotein patterns, parallel with gross hypercholesterolemia and hyperlipemia. Molecules of classes S_f 10–20, S_f 20–100, S_f 100 and greater appeared in the serum in progressively increasing concentrations. Concomitant with these lipid and lipoprotein alterations, aorta atherogenesis was accelerated and intensified, and coronary lesions were routinely found.

In depancreatized cholesterol-fed cockerels, the adrenal steroid hydrocortisone (compound F of Kendall) effected a slight rise in S_f 10–20 levels and a marked elevation of S_f 20–100 and greater. These changes were paralleled by steroid-induced intensification of hypercholesterolemia and hyperlipemia in these steroid diabetic chicks. Despite this serum lipid pattern, aorta atherogenesis was not intensified, and coronary atherogenesis was moderately suppressed.

In intact cholesterol-fed cockerels, estrogen had no effect on cholesterol-induced elevation of plasma lipid and alpha-, beta-lipoprotein patterns. Nevertheless, the hormone was effective both prophylactically and therapeutically against coronary atherogenesis. Moreover, this freedom from coronary lesions was also present in cholesterol-fed cockerels given estrogen plus testosterone, although this hormone combination markedly intensified hypercholesterolemia and elevation of serum lipoproteins of classes S_f 3–8, S_f 10–20, and S_f 20–100 and greater.

These studies indicate: (1) In the chick, as in other species, the hypercholesterolemia and atherogenesis of cholesterol feeding are paralleled by the emergence of low density serum lipoproteins. (2) A hormone-induced dissociation may be effected between high serum levels of lipids and of low density lipoproteins (classes S_f 10–100) on the one hand, and coronary atherogenesis on the other.

14 The Degree of Coronary Atherosclerosis in Bilaterally Oophorectomized Women

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Common acceptance of the observation that there is a marked disparity in the average degree of coronary atherosclerosis between men and women of comparable ages has prompted the study of the degree of coronary atherosclerosis in castrated women.

In a study of cases of bilaterally oophorectomized women who had come to necropsy, 49 cases fulfilled the criteria acceptable for this study. The criteria were (1) an interval of at least two years between oophorectomy and death, (2) menopause not occurring prior to oophorectomy, and (3) age at oophorectomy less than 45 years regardless of menstrual history. In each case, the heart was available for study regarding the state of the coronary arteries.

The degree of coronary atherosclerosis in each decade was greater than in a control series of 600 hearts of women studied by Ackerman and his associates, but it was less than in a control series of 600 hearts of men studied previously by White and his associates.

It has been reported previously that the livers of men with cirrhosis fail to inactivate normally occurring estrogens. A preliminary study of the degree of atherosclerosis in the

coronary arteries of 59 men with cirrhosis of the liver compared with control studies by Ackerman and his associates and by White and his associates disclosed a lower degree of atherosclerosis as compared with the control study on men and at some ages lower than the values in women. It appears that estrogens may play a role in the complicated metabolic matrix representing the pathogenesis of atherosclerosis.

15. Digitonine Precipitation as a Method for Improving the Specificity of the Schultz Test

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In studying atherosclerosis, it is frequently desirable to demonstrate cholesterol in tissue sections. The Schultz test is commonly used for this purpose. This test is not entirely specific for cholesterol. It has been shown recently that carotenes will give a color reaction that is indistinguishable from that produced by cholesterol.

A method has been devised to improve the specificity of the test. Digitonine precipitation, with subsequent acetone extraction of the tissues, is used. The precipitated cholesterol digitonide is not removed by the acetone while other compounds that give a color reaction in the Schultz test are removed.

A series of 24 compounds that give a color with the usual Schultz test have been examined by the modified method. After digitonine precipitation and acetone extraction cholesterol alone gives a color reaction with the Schultz test.

16. Plasma Heparin and Atherosclerosis

Hyman Engelberg

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The role of the serum lipids and lipoproteins in atherosclerosis, and the shift from large lipoprotein molecules to smaller molecules after the injection of heparin, suggest that heparin may normally function in the serum transport phase of fat metabolism. Alterations in the level of plasma heparin may be involved in lipid metabolic defects, and so be of importance in the genesis of atherosclerotic disease. Accordingly, the plasma heparin level was determined in men 30 to 60 years of age with a proven history of myocardial infarction, and in a comparable group of men who had no signs of atherosclerosis. The methods used were the anticoagulant heparin assay technic described by Freeman and Engelberg, the metachromatic method of Gibson, and the procedure of Meneghini and Cervini. The serum cholesterol and phospholipids were also determined. The serum lipoproteins were ultracentrifugally analyzed in both groups at the University of California at Berkeley. The results of these analyses in relation to the plasma heparin level will be presented. Normal heparin levels at various ages and in both sexes will be presented.

17. The Distribution of the Vasa Vasorum of Arteries

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The distribution of the vasa vasorum of arteries was studied by the injection method of Williams (Anat. Rec. **100:** 115, 1948), and by the alkaline phosphatase method of Scharrer (Anat. Rec. **107:** 319, 1950). In the human coronary arteries and aortas the capillaries of the vasa vasorum were found in the outer and middle thirds of the media, only rarely in the inner third. The arterioles arising in the intima usually pass through the inner third of the media without branching. Capillaries are almost never found in the normal intima. Occasionally, there are capillary nets in the thickened intima of arteriosclerotic lesions.

In the arteries of dogs vasa vasorum arising from the intima are rare. A few such vasa are found in the transverse portion of the aortic arch, none in the coronaries. In the rabbit and guinea pig vasa vasorum appear to be limited to the outer third of the media. Experimental arteriosclerotic lesions are frequently seen in arteries too small to have vasa vasorum. Interference with the circulation of the arterial wall appears to accelerate the development of arteriosclerotic lesions.

18. Histochemical Studies of 5-Nucleotidase Activity in Human Aorta. I. Age and Regional Variations

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Further histochemical studies of the enzyme 5-nucleotidase in the human aorta, as demonstrated by the method of McManus, Lupton and Harden, are reported. The occurrence of this enzyme in blood vessels has been described by Reis with gross chemical methods and histochemically by Gomori, by Newman and co-workers, by Reis and Pearse, and by McManus, Lupton and Harden as well as by McManus, Lupton and Etheridge. The specificity of the enzyme has been demonstrated in previous studies by McManus and Lupton with abnormal human kidneys and by Bragdon and McManus with the venom gland of the western diamond-back rattlesnake, *Crotalus atrox*.

The present report describes the variation in histochemically demonstrable 5-nucleotidase activity in the aortas of different ages. The aorta has been studied in sections at different levels. In preliminary studies the amount of 5-nucleotidase histologically demonstrable in the human aorta appears less in the pre-adolescent and adolescent groups than in the older age groups. The relationship of 5-nucleotidase to other normal and abnormal constituents of the aorta will be discussed.

19. Pathologic Changes of Endothelium Demonstrated by Impregnation with Silver Nitrate

Rudolf Altschul

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The impregnation of intercellular spaces with silver nitrate (v. Recklinghausen-Hoyer) which has been used to demonstrate the outlines of normal endothelial cells appears to be

a valuable method in the study of vascular diseases. In comparison with other silver methods which are often "moody" the silver nitrate technic is relatively dependable. It is advisable to study thin (8 micron) as well as thick (40 micron) sections.

In experimental cholesterol arteriosclerosis, this method lends support to prove the much debated origin of foam cells from endothelium. Furthermore, the exact outlining of the boundaries of the endothelial cells and of the cells originating from them shows that many cells are binucleated and even multinucleated. The lack of mitotic figures, to account for the multiplication of nuclei, supports the conclusion previously drawn (Altschul; Kuntz and Sulkin) that in arteriosclerosis amitosis is a frequent phenomenon. This, of itself, is an indication of the poor condition to which the cells have been exposed.

Owing to the slower development of changes in human arteriosclerosis, the silver nitrate impregnation gives here more complicated results the analysis of which is in progress.

20. Surface Studies of the Early Development of Cholesterol Atherosclerosis in the Rabbit

Elizabeth V. Lautsch, Gardner C. McMillan, and G. Lyman Duff

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Technics that make it possible to observe large areas of the aortic intima microscopically from the endothelial surface were employed to study the early development of atherosclerotic lesions in the rabbit.

In rabbits fed daily 1 Gm. of cholesterol and 6 Gm. of vegetable oil mixed with their food, significant elevation of the blood cholesterol and of other blood lipids was detected within four days. It was found that sudanophilic droplets of fat were deposited in the subendothelial ground substance of the intima after only four days of feeding. This lipid was subsequently phagocytosed by macrophages normally present in the intima that appeared at first singly and after seven to nine days in clumps. The development of plaques could be observed in detail. Some of the lining endothelial cells were found to contain a few minute droplets of fat but there was no progressive accumulation of lipids in endothelial cells. Careful study has failed as yet to disclose any other morphologic abnormality of the lining endothelial cells or of their intercellular cement substance. The technics employed give promise of resolving some of the controversies relative to the early stages of development of atherosclerosis in both experimental animals and man.

21. Histochemical Studies of the Early Lesions of Cholesterol Atherosclerosis in the Rabbit

Igor Klatzo, Gardner C. McMillan, and G. Lyman Duff

Department of Pathology, Pathological Institute, McGill University, Montreal, Canada

Sections of the aorta and other organs of normal and of cholesterol-fed rabbits were studied histochemically to determine their lipase and dehydrogenase activity, their fat content, anisotropic lipid and free cholesterol, and the state of the aortic ground substance.

In rabbits fed daily 1 Gm. of cholesterol and 6 Gm. of vegetable oil mixed with their food,

the content of cholesterol and other lipids in the serum was significantly increased after only four days of feeding and continued to increase until high levels were attained. It was observed that there was an increase in the ground substance of the intima and adjacent media after only four days of feeding. Lipase activity was noted in the adrenal cortex after only a few days of feeding and was strongly developed in the adrenal glands and lungs after a week or two of cholesterol consumption. The foam cells in early atherosclerotic lesions of the aorta were lipase positive and showed definite dehydrogenase activity. Free cholesterol was not demonstrable in the very early atherosclerotic lesions but appeared only after the lesions had existed for several days. In more advanced atherosclerotic plaques the presence and distribution of lipase activity was irregular. There was some evidence of an inverse relationship between deposits of free cholesterol and lipase activity in the aorta, adrenal glands and liver.

22. Factors Affecting the Distribution of Vascular Disease in Hypercholesterolemic Rabbits

George M. Hass, Frank B. Kelly, Jr., and C. Bruce Taylor

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In the study of old and young rabbits made hypercholesterolemic by dietary means it was found that the young animals developed aortic atherosclerosis more readily than old animals under the same conditions. The principal localization of the atheromatous disease in both young and old animals was in the aorta and the coronary arterial system. There was no evidence that the degree of involvement of the coronary arterial system could not be positively correlated with the degree of involvement of the aorta. In most cases a better prediction of the magnitude and elevation of the blood cholesterol could be made from an estimate of the severity of the coronary arterial rather than aortic atherosclerosis. Pulmonary atherosclerosis was commonly encountered at all ages but the amount of disease here was never as great as in the coronary arterial system. Furthermore, the pulmonary arterial disease was restricted principally to the intima of the large vessels while small branches of the coronary arterial system were usually severely involved. The only arteries in the peripheral vascular system in which conspicuous lesions were encountered were the intramuscular branches of the pyloric and duodenal vessels. There was little or no vascular disease within the parenchyma of the organs other than the heart.

Among these animals that developed severe amyloid disease of the kidneys, no correlation could be made between the degree of renal involvement, the severity of atherosclerosis or the level of the blood cholesterol. The only means by which significant medial disease of atheromatous nature could be produced was by producing degeneration of the media of the peripheral muscular artery. Under these conditions the medial involvements were characterized by severe atherosclerosis without calcium deposition. In the animals with normal cholesterol levels, calcium deposits, frequently in conspicuous amounts, were found in the areas of medial injury. These observations taken together indicate that a proper appreciation of the relationship between human degenerative vascular disease and experimental hypercholesterolemic vascular disease must take into account the anatomy, function and distribution of the arteries.

23. Atherosclerosis in the Dog. A Comparison of Spontaneous and Experimental Lesions

Stuart Lindsay and I. L. Chaikoff

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1. The present report deals with a study of the cardiovascular system in a group of 26 normal dogs, 14 of which were over 8 years of age, and in a group of 22 dogs which had been subjected to hypophysectomy and thyroidectomy. The purpose of the report is to compare and illustrate arteriosclerotic lesions in the two groups of dogs.

2. The basic aortic lesion in both groups is characterized by an early degeneration of the internal elastic membrane associated with deposition of mucoid ground substance. This is followed by progressive proliferation of intimal connective tissue.

3. Lipid infiltration of the aortic intimal plaques is a secondary phenomenon. It occurs in normal dogs but is more pronounced in hypophysectomized-thyroidectomized dogs which have a high level of blood lipids.

4. In normal dogs, lesions of the coronary arteries are fibrous in origin and do not contain lipids.

5. In hypophysectomized-thyroidectomized dogs, lesions of the coronary and other muscular arteries are primarily lipid in origin and are characterized by foam cell plaques resembling those produced in the dog by feeding of thiouracil and cholesterol.

24. Analysis of Aortic "Arteriosclerosis" in 300 Consecutive Autopsies

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The aortas from 300 consecutive autopsies were analyzed from the viewpoint that aortic arteriosclerosis is a disease which develops in episodic fashion as a result of intermittent insults to the aortic wall, and which leaves anatomic changes that differ somewhat according to the number of such injuries. The analysis consisted of classifying the aortas according to whether they had no lesions of any kind; only atheromata (interpreted as "single crop" lesions); atheromata and pearly plaques (interpreted as "double crop" lesions); or both of the preceding plus calcification, ulceration, etc. (interpreted as "multiple crop" lesions, the number of crops being impossible to determine).

There was no definite correlation between prevalence of aortic arteriosclerosis and race, sex, or body weight. The earliest atheromata were seen at 1½ years. They were observed in all persons beyond the age of 7 years, yet one Negro woman had reached the age of 78 years with only atheromata and no evidence of more than one such crop. Charting the classified aortas against age showed interesting variations in the development of lesions with age, particularly an increase in the rate of development of multiple crops in the period from 45 to 55 years.

While this study was being conducted, it became apparent that one of the most provocative questions was the validity of the assumption that pearly plaques represent the next stage in the progression of some atheromata. The data collected are not only compatible with this idea but also suggest that gross pearly plaques in the aorta are always preceded by atheroma.

25. Relationships between the Levels of Dietary, Liver, and Serum Cholesterol and Hepatic Cholesterol Synthesis

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Gould and Taylor have shown that in the dog and the rabbit, addition of cholesterol to the diet causes a depression of synthesis of cholesterol in the liver (Federation Proc. **9**: 179, 1950; Circulation **2**: 467, 1950). In the present experiments, these observations were extended to another species, the rat, and the degree of depression was found to be related to the liver cholesterol content.

Twenty-four weanling Sprague-Dawley rats were divided into four groups of six rats each. The rats in groups C and D were each given 500 microcuries of I^{131}. One per cent cholesterol was added to the diets of groups B and D. After periods of from one to five weeks, comparisons were made of the ability of liver slices from the various animals to synthesize cholesterol from C^{14} carboxyl-labeled potassium acetate. High cholesterol feeding alone produced no significant change in the serum cholesterol, but resulted in a doubling of the liver cholesterol. Feeding combined with damage to the thyroid gland was followed by an average rise of 80 per cent in serum cholesterol and a trebling of liver cholesterol. When, for all groups, the logarithm of the rate of cholesterol synthesis was plotted against the liver cholesterol content, an approximately linear relationship was found, over a thousand-fold range of synthetic rates.

26. Idiopathic Hypercholesteremia: Frequency in a Hospital Population and in the Families of Hypercholesteremic Index Patients

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This report summarizes studies on idiopathic hypercholesteremia in 250 male and 350 female consecutive hospital admissions and an analysis of the families of the 75 probands who were found to have idiopathic hypercholesteremia (serum cholesterol over 279 mg. per 100 ml. by the Sperry-Schoenheimer method). The age of the 250 men in the index group averaged 50.2 years and their serum cholesterol averaged 215 mg. per 100 ml. The 250 women averaged 48.1 years, and their serum cholesterol 230 mg. per 100 ml.

Ninety-seven of these 500 probands, 41 men and 56 women, were hypercholesteremic. Their average age was 52.8 years, their average serum cholesterol was 348 mg. per 100 ml. Twenty-two of these 97 patients had diseases associated with hypercholesteremia and were excluded from further consideration. Of the remaining 478 probands, 32 of the 242 males (13.2 per cent) and 43 of the 236 females (18.2 per cent) were hypercholesteremic. The frequency of idiopathic hypercholesteremia among the 478 index patients was 15.7 per cent and was not significantly different between the sexes.

A thorough attempt was made to examine the immediate relatives of the 75 hypercholesteremic patients. No relatives of 16 of these probands could be examined. There was no living family member, or those living were scattered throughout the world and not avail-

able. Ninety-seven sibs and 109 children of the remaining 59 hypercholesteremic probands were studied. The frequency of hypercholesteremia among the sibs was 51.5 per cent and among the children it was 29.4 per cent. Both frequencies are significantly higher than found among the 478 patients. The analyses were repeated using data of Keys and co-workers in which age is taken into consideration. The frequency of hypercholesteremia for the total usable sample according to this method of analysis, was 13.2 per cent; the frequency among the sibs of the hypercholesteremic probands was 42.1 per cent and among the children 35.4 per cent. These frequencies are again significantly greater than those found for the index patients; but are not significantly different from the corresponding values obtained when levels of cholesterol greater than 279 mg. per 100 ml. were considered to represent hypercholesteremia.

Of the 478 probands, 266 were Jewish and 212 were not. Hypercholesteremia was significantly more frequent among the Jewish probands (21 per cent versus 9 per cent), but the frequency among sibs and children was not different when Jewish hypercholesteremic probands and families were compared with non-Jewish.

Although no definite conclusions can be drawn from these data, it may be tentatively stated that, if genetic determination is involved, idiopathic hypercholesteremia in the families of hypercholesteremic probands may be determined by a dominant gene with incomplete penetrance.

27. Presenile Medial Calcinosis of the Arteries of the Extremities

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Two cases are presented to illustrate a rather uncommon form of arteriosclerosis which is characterized by extensive calcinosis and sometimes formation of bone in the medial coat of the arteries of extremities of middle-aged persons.

The first patient, a middle-aged man, 38 years, had minimal fatigue of the legs that was vaguely suggestive of intermittent claudication. Arterial pulsations were markedly impaired in both upper and lower extremities and roentgenologic examination showed extensive calcinosis of the large arteries. There was no evidence of diabetes, and the concentration of plasma lipoids was normal. The patient was observed repeatedly for seven years during which he did not have any further symptoms referable to the circulation nor any roentgenologic evidence of progression of the arterial lesions.

The second patient was also a man of 38 years of age, who had definite intermittent claudication with marked impairment of arterial pulsations in the popliteal, posterior tibial and dorsalis pedis arteries and absence of pulsation in the ulnar arteries. Roentgenograms of the extremities also showed extensive calcinosis of the large arteries. Biopsy of one ulnar artery showed the medial coat to be almost completely replaced by large deposits of calcium and bone. There was no evidence of atheroma. The etiology of this condition is unknown. The appearance of the lesion suggested that probably the condition had been present for many years and possibly developed in childhood. The roentgenographic appearance of the arterial calcification differs from that of typical Moenckeberg's sclerosis and that of calcareous atherosclerosis.

28. Cation Content of the Aorta Wall in Renal and DCA Hypertension

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In a group of rats with severe renal hypertension, the aorta stripped of adventitia contained 34 per cent more water,† 16 per cent more sodium,† 42 per cent more potassium,† and 13 per cent less magnesium† than similarly prepared aortas from normotensive rats. Even rats with the kidney operation that did not develop hypertension showed 7 per cent more water,† 20 per cent more potassium,† and 6 per cent less magnesium than normal. In contrast, the chemical composition of brain and muscle in these rats exhibited no or relatively minor changes.

Rats with desoxycorticosterone acetate hypertension showed chemical alterations in the aorta in the same direction, 20 per cent more water,† 22 per cent more sodium,† and 15 per cent more potassium.†

If the higher water content of the hypertensive aorta extended to the arterioles, the swelling of the arteriolar wall would encroach on the lumen enough to double peripheral flow resistance.

Low sodium diets may reduce blood pressure in hypertensive states by decreasing arterial sodium concentrations to more normal levels.

* Established Investigator of the American Heart Association.

† Statistically significant difference.

29. Vascular Lesions Elicited by Renin in Nephrectomized Dogs

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Injection of renin in desoxycorticosterone-pretreated rats precipitates a syndrome associated with widespread renal and vascular lesions. The vasculotoxic properties of renin were explored in dogs, bilaterally nephrectomized, and maintained on 1 per cent sodium chloride. Renin (200 to 300 Goldblatt dog units) was subcutaneously injected in three divided doses over 24 hours.

The animals given renin showed increased arterial pressure and edema and predeceased the controls. At autopsy, both controls and renin-treated dogs showed hemorrhages; after renin, these were more intense and widespread. Renin treatment was also associated with anasarca.

On microscopic examination, about 10 per cent of controls showed arteriolar necroses; after renin, these were much more severe and diffuse. The necrosis involved the media, while elastica and intima were usually intact. Medial and peri-adventitial tissues were infiltrated with a coagulum which stained bright red with trichrome, dark blue with phosphotungstic hematoxylin and blue with periodic acid-fuchsin. Some vessels of capillary size were occluded by colloid-looking thrombi.

In brief, administration of renin and sodium chloride to nephrectomized dogs elicits lesions similar to those which appear in some nephrectomized dogs maintained by artificial means.

30. Vascular Response in Local and Systemic Circulation to Various Sympatholytic and Vasodilator Drugs Following Peripheral Cold Injury

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A range of cold injury produced varying degrees of local, systemic and vascular changes. The circulation in the exteriorized rabbit kidney was tested by the injection of various dyes

into the ear vein. After solid freezing of the leg, intravenous dye failed to enter the kidney. All tests of drug effects on renal circulation were done while the leg was frozen solid. Tubulin administration was followed by complete filling of the kidney with dye. Hexamethonium, Priscoline and hydrazinophthalazine resulted in a patchy entrance of the dye into the kidney, but hydrazinophthalein caused shrinking of the kidney as shown by marked capsular wrinkling. Benodaine also produced shrinking of the kidney but renal vascular spasm was unaffected. Histamine, acetylcholine, and Hydrergine failed to release the renal vascular spasm following frostbite. The blood flow in the area directly exposed to the frostbite was studied with and without Tubulin administration. The dye entered the frozen extremity in one third the time in the Tubulin-treated animal compared with the control. Tubulin-treated animals, both pre- and postperipheral cold injury, were protected against tubular lesions found in our untreated animals and previously reported by Erastow, and by Lewis and Thompson.

31. The Effect of Aureomycin on Serum Lipids and Vascular Lesions in Cholesterol Fed Rabbits

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Twenty immature female rabbits were divided into four groups. Groups I and III received 0.5 per cent, groups II and IV, 1 per cent cholesterol in their diet. Aureomycin (0.025 per cent) was also added to the diets of groups III and IV. In the 20 weeks of the experiment all groups ate about the same amount of food and showed similar weight gains.

Histologic examination was made of 18 different organs, and the animals were rated on the extent and severity of the vascular and parenchymal lesions observed. The following serum analyses were made: total and free cholesterol, total lipid, lipid phosphorus, nonprotein nitrogen, and inorganic phosphate. Liver fat was also determined.

In the animals ingesting 1 per cent cholesterol the vascular and parenchymal lesions were more severe than in animals receiving 0.5 per cent. They also showed a significantly greater elevation of serum lipid and cholesterol, and of liver fat. Addition of aureomycin increased the serum lipids and accentuated the vascular and parenchymal lesions.

32. The Effect of Cortisone and ACTH on Experimental Cholesterol Atherosclerosis in Rabbits

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The effect of cortisone and adrenocorticotropic hormone (ACTH) on the production of aortic atherosclerosis in normal and cholesterol-fed rabbits was studied. In addition, the effect of these agents on the serum cholesterol and phospholipids was also observed.

Five rabbits received 10 mg. of cortisone intramuscularly three times weekly for 10 weeks. No significant effect on the serum cholesterol was noted but a definite increase in the serum phospholipids occurred. Five rabbits were injected with 5 mg. of ACTH three times

weekly for 10 weeks. No effect on the serum cholesterol or phospholipids was noted. Atherosclerotic lesions did not develop in any of the rabbits in these two groups.

Eight rabbits were fed 3 to 5 Gm. of cholesterol in divided doses, weekly. The hypercholesterolemia produced by cholesterol feeding was accompanied by a progressive reduction in the phospholipid-cholesterol ratio. Macroscopic atherosclerosis developed in four of these animals.

In each of 13 cholesterol-fed rabbits, the administration of cortisone inhibited the formation of aortic atherosclerosis even though the hypercholesterolemia was accentuated and the phospholipid-cholesterol ratio was markedly depressed. ACTH was also anti-atherogenic but not to the same degree as cortisone. Two out of 10 cholesterol-fed rabbits developed macroscopic aortic atherosclerosis while receiving ACTH.

33. Peripheral Neurectomy for Pain in Obliterative Arterial Disease

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An appraisal of results of peripheral neurectomy in the relief of pain resulting from arteriosclerosis obliterans and thromboangiitis obliterans of the lower extremities is given. The pertinent literature is briefly reviewed and a summary of our own observations presented. Orebaugh and Gustafson, in evaluating results in 61 patients operated upon at the University of Michigan Hospital for intractable pain, included 45 patients with arteriosclerosis obliterans and 16 patients with thromboangiitis obliterans. The tibial nerve, superficial and deep peroneal nerves, sural nerve and saphenous nerves were interrupted usually at the junction of the middle and lower one-third of the leg and the anesthesia used was either general or spinal.

Our experience with peripheral neurectomy re-emphasizes that there is marked discrepancy both with regard to relief of pain and the incidence of major amputation in these two major groups of obliterative peripheral arterial disease.

In general, peripheral neurectomy is a valuable operative procedure for the relief of pain in selected cases of thromboangiitis obliterans but should be abandoned in treating patients with arteriosclerosis obliterans. In this latter disease, only a small percentage of patients will receive relief of pain or will avoid major amputation as a result of peripheral neurectomy.

34. Genetic Studies on Coronary Atherosclerosis Developing After Age 60

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This study is concerned with a group of 100 unselected patients with coronary artery disease whose symptoms began after age 60. The average age at onset was 63.4, and the average age at time of study was 65.8 years. The average serum cholesterol level (by the Sperry-Schoenheimer method) was 279 mg. per 100 ml., ± 4.67 (standard deviation of the mean). It was lower than in a previously studied group of patients whose symptoms of coronary artery disease started before age 50 and whose average age at onset of symptoms was 42 and at time

of study 45 years. This is significant because in normal persons, according to Keys and coworkers, the mean serum cholesterol level is almost identical at ages 45 and 65 (235.5 mg. per 100 ml. at 45, and 236.7 mg. at 65).

Family studies of older patients are difficult. Only 28 families of the 100 probands could be examined partially. Of the 52 siblings studied, 25 (or 48 per cent) had serum cholesterol levels over 280 mg. per 100 ml. The frequency distribution of serum cholesterol levels of the probands and of their siblings showed a striking parallelism. The variation of serum cholesterol level with age was also seen in the sibs. This was evident although the readings tended to be higher than those of normal persons.

The study suggests that the derangement of lipid metabolism, manifesting itself as hypercholesteremia, of patients whose coronary artery disease begins after age 60 represents a more indolent metabolic disturbance than that encountered in the younger patients affected with this disease. However, the incidence of hypercholesteremia among the sibs of the older group does not differ significantly from that of the sibs of the younger group.

35. The Assay of Plasma Heparin, Using Anticoagulant Activity as a Measure of Heparin

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With the demonstration of the effect of heparin upon serum lipoproteins, and the possible role of heparin in fat metabolism, the need for a satisfactory method of determining the level of plasma heparin arises. Published methods are based upon the metachromatic activity of heparin, but suffer from the fact that they determine the level of all metachromatically reacting substances in plasma. Furthermore, anticoagulant activity has not been demonstrated, and so the presence of heparin has only been inferred, not proved.

In this investigation, anticoagulant activity was assumed to be the most reliable measure of heparin. Modification of existing technics has led to a method yielding a plasma extract which gives such activity. The method of assay of the anticoagulant activity is a modification of the U. S. P. IV method for smaller amounts of heparin.

36. The Effect of Choline on the Serum Cholesterol and Phospholipids in Patients with Coronary Artery Disease

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Eleven patients (10 males and 1 female) were selected for study. Their ages ranged from 29 to 57 years. Nine subjects had coronary insufficiency or previous myocardial infarction, or both; two patients were suspected of having coronary artery disease and were members of a family with a striking history of arteriosclerosis. No dietary restrictions were imposed. Length of study ranged from 5.5 to 13 months.

The preliminary control studies extended from one to five months and at least three estimations of serum cholesterol and phospholipids were done. Choline (4 Gm. daily of choline base) was given orally in divided doses for periods ranging from one to five months; these were alternated with control periods ranging from one to six months when no choline was given. The serum lipids were estimated

during and at the end of both the control and experimental periods. A total of 80 estimations of the serum lipids were done during this study.

All determinations were done in duplicate. The phospholipids were determined by a modified Whitehorn method and cholesterol by the Schoenheimer-Sperry method.

The results indicate that choline therapy was without effect on the concentration of serum cholesterol, phospholipids, or phospholipid-cholesterol ratio.

37. Arteriosclerotic Popliteal Aneurysm: A Clinical Follow-up Study

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Sixty-nine patients who had a total of 100 popliteal aneurysms were followed. These patients were seen at the Mayo Clinic from 1919 through 1950. Arteriosclerosis was the cause of 91 of the aneurysms, arteriosclerosis and syphilis were the cause of four aneurysms, and arteriosclerosis and brucellosis were the cause of one aneurysm. Satisfactory data were obtained concerning 67 patients with 97 aneurysms, and complete information (that is, until death of patient or until October, 1951) was obtained in 62 patients with 90 aneurysms. Twenty-one aneurysms were treated surgically at the first visit of the patients, and follow-up data regarding 20 of these were obtained. The average period of follow-up study from the time of diagnosis at the Clinic was 50 months. The longest period was 318 months, and the shortest was 11 days in a case in which the patient died shortly after diagnosis was made.

Follow-up information was available on 70 of 73 aneurysms treated conservatively. Five of these aneurysms later came to surgery. Of the 70 aneurysms, 23 or 32.8 per cent caused subsequent complications on conservative treatment, and 11 or 15.7 per cent necessitated amputation, subsequently. Five of 50 patients treated conservatively died as a direct result of complications of the aneurysm.

Twenty-one aneurysms in 19 patients were treated surgically at the first visit. All extremities survived. There were no further complications and no deaths attributable to the aneurysm during the follow-up period in this group. Five aneurysms were treated surgically at a latter date and three of the five were operated upon elsewhere. Amputation was necessary postoperatively because of gangrene in the case of two of the five aneurysms.

Twenty-five aneurysms with complications (such as thrombosis of the aneurysm, embolism distal to aneurysm, leakage or rupture, and compression of veins or nerves) were treated conservatively, and 21 aneurysms with complications were treated surgically. Of the group treated conservatively, 10 (40 per cent) had subsequent complications, and six (24 per cent) necessitated amputation in the follow-up period. Of the 21 aneurysms treated surgically, two (10 per cent) necessitated amputation immediately after the operation. None of the remaining 19 caused further complications or necessitated amputation in the follow-up period.

These data indicate that many patients with popliteal aneurysm who are treated conservatively are likely to have serious complications from the aneurysm, particularly if complications are already present, whereas those treated surgically, especially if treated early, are unlikely to lose an extremity or to have complications.

38. The Ratio Between Phospholipid and the Cholesterol of Blood as an Index of Human Atherosclerosis

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It has been suggested that there may be a relationship between the fixation of lipid in intimal cells and decreased phospholipid-total cholesterol ratios in blood serum. Growing

interest in this ratio as an index of atherogenesis led us to draw up and apply to this ratio six critical questions: (1) Do the two substances exist biologically? (2) Is there a demonstrable relationship between them? (3) How is this relationship altered in diseases which are the manifestation of atherosclerotic vascular changes? (4) How is this relationship altered in diseases which predispose to atherosclerosis? (5) Are there diseases which show this same abnormality but are not associated with an unusual degree of atherosclerosis? (6) Is there any other explanation for these alterations which have been observed?

It was concluded that the relationship between phospholipid and the cholesterols of blood serum is such that this ratio can be no more useful as an index of atherosclerosis than the discredited total cholesterol value itself.

39. Effect of Testosterone and Chorionic Gonadotrophin on Estrogen-induced Inhibition of Coronary Atherogenesis in Cholesterol-Fed Cockerels

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This study was undertaken to determine the effect of testosterone and chorionic gonadotrophin on the previously demonstrated estrogen inhibition of coronary atherogenesis in cholesterol-fed young cockerels. Two series of experiments were undertaken, in both of which all groups were fed a mash supplemented with cholesterol (series I, 2 per cent, series II, 1 per cent) plus 5 per cent cottonseed oil. The two groups were: Series I—(1) control, no hormone; (2) estrogen (1 mg. per chick, per day); (3) testosterone (0.2 to 1.0 mg. per chick, per day); (4) testosterone plus estrogen. Series II—as in series I, but with larger dose of testosterone (0.2 to 0.3 mg. per chick, per day); and with two additional groups, (5) chorionic gonadotrophin (pregnant mare's serum—P.M.S.) (100 to 400 I.U. per chick, per day); and (6) chorionic gonadotrophin plus estrogen. The testosterone dosage was adequate in this second series to reverse the feminizing effect of estrogen on combs.

Testosterone alone and chorionic gonadotrophin alone (at hyperandrogenic dosage levels) were without significant effect on levels of cholesterolemia, phospholipemia and cholesterol-lipid phosphorus (C/P) ratios in these cholesterol-fed cockerels. Correspondingly, they failed to exert a definite influence on cholesterol-induced aorta or coronary atherogenesis.

The groups of hormone combination also exhibited a hypercholesterolemia similar in degree to the control group and to the groups receiving individual hormones. Like chicks receiving only estrogen, cockerels on hormone combinations had markedly intensified hyperphospholipemia, with resulting depression of elevated plasma cholesterol-lipid phosphorus (C/P) ratios toward normal levels. Further, as in chicks receiving estrogen alone, these birds exhibited prophylactic inhibition of coronary atherogenesis, with no associated retardation of aorta atherogenesis.

It is concluded: (1) Hyperandrogenism, induced by testosterone or chorionic gonadotrophin, does not grossly intensify aorta or coronary atherogenesis in young cholesterol-fed cockerels. (2) Neither testosterone nor chorionic gonadotrophin in large doses (adequate to counteract estrogen feminization) reverse estrogen prophylactic inhibition of cholesterol-induced coronary atherogenesis.

40. In Vitro Lipoprotein Transformations

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The acute in vivo effect of heparin in man is the reduction or the complete wipeout of lipoprotein molecules of the S_f 20–40,000 classes. As one approach to the understanding

of the in vivo mechanism of normal lipoprotein transformation as well as the dramatic transformations induced by heparin, interactions of various fractions from the blood of heparinized individuals with isolated lipoproteins of the low-density group were studied in vitro. In these studies isolated S_f 20–200 class lipoproteins have been transformed in vitro to lower class lipoproteins by reaction with an active fraction from postheparin plasma. This active fraction is the bottom fraction from a 1.063 density preparative ultracentrifugal run in which the density increment is achieved with D_2O (heavy water). The large molecules present in the active fraction consist of all the serum proteins and lipoproteins of density greater than 1.063 Gm. per cubic centimeter, among which are the two major high density lipoproteins of approximate hydrated density of 1.08 and 1.12 Gm. per cubic centimeter, respectively.

Incubation of the S_f 20–200 class lipoproteins with this active fraction in vitro results in the lowering or the wipeout of the molecules in the S_f 20–200 class and in the appearance, de novo, (although not fully compensatory) of lipoproteins of the S_f 4–20 class. A study of S_f rate versus solution density demonstrated a change in approximate hydrated density from 0.98 Gm. per cubic centimeter for the reactant S_f 20–200 class molecules to approximately 1.02 Gm. per cubic centimeter for the product S_f 4–20 class lipoproteins. The approximate magnitude of the densities involved and the density shift are consistent with the hypothesis that the in vitro produced S_f 4–20 lipoproteins may be identical with or closely similar to the S_f 4–20 lipoproteins which occur in human serum. In addition to the change which occurs within the low density group of lipoproteins there is evidence that the high density lipoproteins also participate in the transformation mechanism. During the in vitro lipoprotein reaction there is also formed an appreciable precipitate, which has been shown to consist mainly of calcium oleate. This finding suggests that the hydrolysis of glyceryl ester may be involved as part of the mechanism of lipoprotein transformation in the presence of the active factor.

That the transformations described occur in vitro suggests that the observed in vivo transformations do not require the participation of the red cells nor the entry into or exit from the vascular compartment of the reacting constituents.

41. The Results of Diet, Medicinal Agents and Emotional Disorders on Serum Phospholipid-Cholesterol Ratios in Coronary Atherosclerosis

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The experimental and clinical studies of Kellner and associates, Ahrens and Kunkel, Gertler, Lerman and White, Morrison and co-workers, and others have shown that the serum phospholipid-cholesterol ratio is a valuable index as to atherogenesis in animals and in humans. In addition to the experimental proof of this fact the clinical observers found that a phospholipid–cholesterol ratio above the unit of 1.0 was usually found in the normal case and a ratio below 1.0 in the presence of active coronary artery disease.

There are presented the results of a three-year study in over 300 cases which investigated the behavior of the serum phospholipid–cholesterol ratio under variations of dietary, medicinal, psychologic, hormonal and controlled conditions.

Included in the data to be presented are the specific changes in serum phospholipid-cholesterol ratio, compared with other serum lipoproteins, as affected by (1) low fat-low cholesterol diets, (2) ACTH and cortisone, (3) lipotropic substances such as choline, betaine, and inositol, (4) soybean and other lecithins, (5) emotional disorders, and (6) intravenous heparin.

It was found that strictly controlled low fat–

low cholesterol diets often favorably influenced serum phospholipid–cholesterol ratios although numerous exceptions were found. Lipotropic agents were highly effective in most cases in restoring previously abnormal ratios below 1.0 to above 1.0. Emotional disturbances in "genetically susceptible" coronary disease in individuals showed numerous instances wherein markedly unfavorable changes took place in phospholipid-cholesterol ratios.

42. Studies on the Fate of C^{14}-Labeled Cholesterol and its Oxidation Products after Intravenous Injection

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In a previous report it was shown that the injection of a colloidal solution containing 0.5 Gm. cholesterol stabilized with sodium stearate into a 2.5 Kg. rabbit led to an increase of 250 to 350 mg. per 100 cc. in the serum cholesterol, 10 minutes after injection. The level in the serum fell rapidly during the first six hours and then rose again. Repetition of this work with cholesterol biologically labeled with C^{14} has shown that much of the injected cholesterol is stored in the liver where it apparently forms part of a readily mobilizable pool of cholesterol.

This work had been done to furnish a baseline for a study of various intermediates which may arise in the catabolism of cholesterol. It has been shown by others that cholestenone may be converted into cholesterol and coprosterol in the body, but no information is available that indicates that it is an intermediate in the normal catabolism of cholesterol. It is hoped that quantitative studies of this and other oxidation products of cholesterol may yield information concerning the process by which the body disposes of cholesterol.

43. Analytic Comparison of Cholesterol, Phospholipids and Ratios

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The material for the 'Analytical Comparison' was derived from a large number of patients seen both privately and in the clinic for diagnostic purposes. Cases under treatment and those with frank diagnosis of diseases associated with abnormal serum lipid levels, such as cirrhosis of the liver, nephrosis, hypothyroidism, xanthomatosis, inanition, and other conditions were excluded. Also excluded were those under heparin treatment for angina pectoris. The series is tabulated according to sex and age by decades. This large series should contribute to the establishment of levels to be expected in the male and female at the different decades of life.

44. Influence of Gonadectomy on Cholesterol-Induced Aorta and Coronary Atherogenesis in Young Chicks

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In view of the well known sex differences in human susceptibility to coronary atherosclerosis prior to age 50, experiments were undertaken on the effects of gonadectomy on cholesterol-induced atherosclerosis in young growing chicks.

Sixty male and 60 female chicks, 13 weeks of age, were maintained for five weeks on a diet

of mash supplemented with 1 per cent cholesterol plus 5 per cent cottonseed oil (1 CO). Two to three weeks prior to the onset of experimental feeding, 30 male and 30 female birds had been gonadectomized. The four sets of 30 chicks each were divided into three groups of 10 chicks each: (1) 1 CO alone; (2) 1 CO plus testosterone (0.2 to 0.4 mg. per chick, per day); (3) 1 CO plus estrogen (1 mg. per chick, per day).

Degree of hypercholesterolemia was comparable in all groups, male and female, castrate and intact, hormone-treated and nontreated, and ranged from 474 to 748 mg. per 100 cc. Correspondingly, aorta atherogenesis was similar in incidence and degree in all groups. Intact untreated females exhibited a low incidence of cholesterol-induced coronary atherogenesis (40 per cent), compared with gonadectomized untreated females (100 per cent) and intact untreated males (100 per cent). All groups receiving estrogen, males and females, intact and gonadectomized, were uniformly free of coronary atherosclerotic lesions.

45. Prevention and Therapeutic Management of Atherosclerosis

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With an increase in the age of the general population, there is an accompanying higher incidence of arteriosclerosis. Also, the death rate from arteriosclerotic heart disease has risen far out of proportion to the general increase in age. This warrants an attempt to prevent, if possible, and to ameliorate, when present, by any means available, the protean ravages of this disease.

Upon the supposition that arteriosclerosis to a greater or lesser extent is almost universal that there is an hereditary tendency in certain families, and that there is usually a higher incidence in diseases characterized by high serum lipids, a treatment has been devised consisting of low lipid–low cholesterol diet, endocrines, enzymes, vitamins and lipotropic agents.

Before age 40, everyone should have a physical and laboratory check-up once a year. Those who have a family history of arteriosclerosis and those who have disorders with high lipids and all past age 40 should be examined twice a year and advised to limit the lipids in the diet. Any other pathologic condition should receive appropriate treatment. Each case must be treated individually. Extreme care must be exercised particularly in older patients to maintain an ideal body weight. The other agents are used as indicated by history, physical examination, hormone assay, basal metabolism rates, liver and gall bladder functional tests, and other studies. After treatment is properly established, there is invariably a sense of well being.

Considering the usual slow formation of atheromatous plaques, definite evaluation of results may not be forthcoming for a number of years. An extremely critical analysis of results must be carried out due to the large number of factors involved.

46. Cholesterol, Antilipfanogen and Fat Deposition

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We are getting evidence that cholesterol ties up antilipfanogen, thereby liberating free lipfanogens, which then cause fat deposition. Final conclusions have not yet been reached.

47. Effects of Adrenal Steroid Compound F on Plasma Lipids and Atherogenesis in Cholesterol-Fed Chicks

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Since human beings with hyperadrenocortical states tend to develop severe atherosclerosis, and since adrenal steroids are being increasingly used clinically for long-term therapy, studies were undertaken on the effects of the corticoid compound F on plasma lipids and atherogenesis in cholesterol-fed (0.5 per cent cholesterol) young cockerels, intact, alloxanized, and depancreatized.

In all groups, administration of compound F (1 to 2 mg. per chick, per day) for five weeks induced: (1) significant retardation of growth and development (despite high level of feed intake); (2) hyperglycemia, slight in the intact and marked in the depancreatized birds (steroid diabetes); (3) intensified hyperlipemia, hypercholesterolemia, hyperphospholipemia. These changes were accompanied by no significant alterations in blood pressure or aorta atherogenesis. In the intact and alloxanized cockerels, hormone treated and untreated, cholesterol-induced coronary atherogenesis was similar in incidence and degree. In both series, the depancreatized, compound F-treated birds exhibited a partial incomplete inhibition of coronary atherogenesis.

48. The Effect of Estrogen on Serum Phospholipid

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To a series of male and female patients, estrogen was given. A majority of these patients was under treatment by diet and lipotropic agents for abnormal serum lipids and more particularly their ratios.

The ratio used is the total phospholipids–lecithin (serum phospholipids × 25) divided by the total cholesterol (free cholesterol plus esters). The normal is considered 1.0 or above; the abnormal below 1.0. It was noted that there was a return to the normal ratio by an elevation of the phospholipid level, in the majority of patients treated with estrogen.

To another group of patients, in whom, on first determination, lipid was found abnormally high, with abnormal ratios, the estrogens were given along with the diet at the beginning of the treatment. The usual variability of these values must be taken into consideration in interpreting their effect on the serum phospholipids.

49. A Comparison of the Chylomicron Index, Serum Total Cholesterol, and Lipid Phosphorus as Indices of an "Atherosclerotic State"

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Cholesterol and lipid phosphorus determinations were made on the fasting serum of 48 patients with myocardial infarction ranging in age from 34 to 86 years. Similar studies were done on 42 normal adults ranging in age from 22 to 65 years. One hundred seven infarction

patients comprised the chylomicron index determination group and included the 48 on whom chemical determinations were made. The 42 normal subjects were also studied for visible darkfield fasting serum fat droplet emulsification (chylomicron index represents the per cent of the visible globules greater than 0.5 micron as seen by 1900 times magnification). Histories were obtained concerning familial illness from all normal adults. All determinations were done by a "blind" technic which prevented knowledge of case histories until all records were completed. Charts suggest the value of these tests—or lack of it—as diagnostic aids in recognition of an "atherosclerotic state."

Mean cholesterol values of 192 ± 41 mg. per 100 cc. and 224 ± 56 mg. per 100 cc. were found in normal and infarction patients, respectively. Mean chylomicron index values of 39.6 ± 8.5 and 59.9 ± 8.8 were found in normal and infarction patients. The difference between the latter two means approximates 10 times the standard error of their difference whereas the difference between the mean cholesterol values is but three times that error. Evidence will be presented suggesting that the simple clinical test for the chylomicron index of fasting serum is more sensitive as an indicator of, and more intimately associated with, the atheromatous state than the chemical determinations used in this study.

50. Studies on the Mechanism of the Regression of Experimentally Produced Arterial Lesions in Dogs

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It has been shown that the arterial lesions produced in dogs which are maintained upon a cholesterol-thiouracil regimen regress when the dogs are returned to a normal diet. It is important to determine whether the cholesterol and other lipids are removed mechanically, being slowly washed out by the movement of the plasma through the arterial walls, or whether the lipids are metabolized in situ. The effect of administration of thiouracil and of thyroid upon the rate of regression has been studied. The thiouracil might be expected to slow down the metabolism of cholesterol and the thyroid to accelerate it. The results to date do not support the view that the regression of the lesions depends upon metabolic factors.

51. The Effect of Heparin and Placebo Therapy in Coronary Artery Disease

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With recent interest in the relationship of serum lipoids and lipoproteins to coronary artery disease reports have appeared showing the beneficial responses to heparin therapy.

The authors studied a group of patients with known patterns of angina pectoris who had been observed for a period of years in the cardiac clinic of the county hospital. Another group of patients was seen in private cardiology practice and were studied with the usual clinical observations. The group of hospital clinic patients were subdivided in two sections, each of 12 weeks therapy; one section received 100 mg. of heparin intramuscularly three times weekly for six weeks and 2 cc. of normal saline solution three times weekly for six weeks; the second section received the same therapy but in reverse order. All patients started therapy

at the same time. The patients, laboratory technicians and clinicians were uninformed of the therapy employed. Weekly visits were made at the clinic at which time laboratory studies and evaluation regarding frequency and severity of attacks were made; data regarding blood pressure, pulse, and untoward effects were recorded. Studies included cholesterol levels, chylomicron counts, lipid phosphorus, and phospholipid-cholesterol ratio determination.

The data revealed that while on heparin therapy, six patients were improved, three were unchanged, five became worse; on normal saline therapy, nine improved, four were unchanged, none became worse. Heparin was discontinued in two patients: one had a possible sensitivity to heparin and one had a possible recurrent myocardial infarction. No significant differences were noted in laboratory studies in heparin or placebo therapy.

Of 14 physicians seen as patients in private practice, none were improved on heparin therapy. Control studies on this group were not made nor were laboratory studies conducted.

52. Classification of Arteriopathies

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Nomenclature Committee of the American Society for the Study of Arteriosclerosis

I. Degenerative Arteriopathies

1. *Atherosclerosis*, that form of arterial disease characterized by intimal atheroma formation leading to restriction of the lumen of the artery and sometimes complicated by thrombotic occlusion.
2. *Medial Arteriosclerosis*, those types of arteriopathies characterized by degenerative changes primarily occurring in the medial coat.
3. *Arterionecrosis*
   a. idiopathic or nonspecific
   b. cystic medionecrosis (Erdheim)
   c. toxic arterionecrosis

II. Productive and/or Hyperplastic arteriopathies

That type of arterial disease showing hyperplasia of the intima and/or media with concommitant changes in the distribution of elastic tissue. A phenomenon often associated with or resulting from increased arterial pressure.

III. Inflammatory Arteriopathies

1. *Arteritis*: any inflammatory condition of any artery. The following etiologic causes have been suggested:
   a. infectious
   b. hypersensitivity (allergies)
   c. chemical
   d. physical reaction to light, thermic conditions, x-ray and other forms of atomic radiation
   e. trauma of mechanical origin
2. *Thromboangiitis Obliterans* (Buerger's disease)

IV. Combined Forms of Arteriopathies, consisting of any combination of the above arteriopathies.